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# ETIOLOGY OF CHRONIC INTESTINAL INDIGESTION

## CHEMICAL AND BACTERIOLOGIC INVESTIGATION *

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AND

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The studies reported in this paper were undertaken in consequence of some clinical and chemical observations made by us on the condition of chronic intestinal indigestion, particularly in relation to treatment with special high protein diets.[1] It seemed desirable to attempt to explain certain apparently contradictory phenomena, and if possible to formulate a rational explanation of the successful use of extremely high protein diets in overcoming this condition.

The first question that comes to mind concerns the well-known characteristics of the typical feces, namely, mushy consistency, often acid reaction, suggesting abnormal fermentative activity in the intestinal tract, but accompanied almost invariably by a markedly putrefactive odor. How are the symptoms of two antagonistic forms of bacterial activity to be accounted for? That a fermentative condition prevails is supported by the abdominal distension characteristic of the condition, and by the exaggeration of symptoms when more carbohydrate is added to the diet. That putrefactive activities are also concerned seems to have been indicated by Herter's [2] findings of indolic and phenolic substances in the urine and of aromatic oxyacids in the feces in chronic intestinal indigestion. Other questions arise in connection with the type of food used to bring about improvement. A high protein diet would naturally tend to overcome the excessive fermentation, but why at the same time does it not encourage the putrefactive processes? Further, the importance of the ingestion of large amounts of a specific organism, namely, *Streptococcus lacticus* (*Micrococcus ovalis*) in the

* Received for publication, June 27, 1925.

* From the Wards and Laboratories of the Hospital for Sick Children, and the Sub-Department of Pediatrics, University of Toronto.

1. Brown, A.; Courtney, A. M., and MacLachlan, I. F.: Brit. J. Child. Dis. **19**:113, 1922.

2. Herter, C., Intestinal Infantilism, MacMillan Co., New York, 1908.

lactic acid or protein milk which always accompanies these diets is not clearly understood. Does this organism play an important rôle in supplanting the existing flora? If so, how is it that this supposedly lactose-fermenting organism is able to establish itself as the predominant form on a low carbohydrate high protein diet?

Herter, in the cases of chronic intestinal indigestion studied by him, claims to have found a fairly typical intestinal flora with gram-positive organisms of the bifidus type predominating. That such a flora, which is abnormal for children established on a mixed diet, characterizes the feces in chronic intestinal indigestion apparently has not been generally accepted. It is certainly not easy to see how the typically lactose-fermenting *B. bifidus* has been able to remain predominant after the milk content of the diet has been materially reduced, nor why it should then produce excessive fermentation and putrefaction in place of its former beneficial effect. Has the organism undergone a transformation, or has it established a symbiosis with some other organism of the putrefactive type? In any case, what were the circumstances under which the pathologic condition arose? It is evident that little progress could be made toward answering the foregoing questions without the aid of a bacteriologist. Accordingly, the present combined bacteriologic and chemical study was undertaken. On the bacteriologic side it was of the first importance to determine to what extent Herter's findings—in regard to a typical flora in chronic intestinal indigestion—were to be confirmed in the cases coming under our observation.

## BACTERIOLOGIC STUDIES

To a certain extent this has been accomplished. The bacteriologic methods pursued have been, in the main, based on those developed by Morris, Porter and Meyer [3] for the differentiation of fermentative and putrefactive stools. This method is fairly complete, and includes the direct examination of the stool smear as well as the qualitative and quantitative study of the aerobic and anaerobic bacteria and spore forms. Smears of the various cultures were examined, and the predominating forms noted, which in many cases were isolated for detailed examination. It is not necessary to repeat here the exact mediums used and the significance of each, but it was found that those which gave the best results were the sugar fermentation tubes. It was hoped that considerable information concerning anaerobic organisms would be obtained from the anaerobic plates made directly from the stool emulsion, but it was found that the *B. coli* group of organisms overgrew all others on these plates.

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3. Morris, G. B.; Porter, R. L., and Meyer, K. F.: J. Infect. Dis. **25**:349, 1919.

Examination of the stool smear was considered of the greatest importance, and the smears of the sediments of the sugar fermentation tubes were of next importance. For isolation of the individual organisms, particularly of the gram-positive group, the best method found was to inoculate some of the sediment of the sugar fermentation tubes on lactose agar, on whey agar, or on dextrose sodium oleate plates for anaerobic culture.

At the beginning, it was thought that possibly some information could be obtained from cultural methods alone. For control purposes a series of stools of infants on various diets was obtained. The most valuable result of this study was the difference noted in the amount of gas produced in sugar fermentation tubes by the stools of infants on these diets (Table 1).

From this table it is interesting to note that the average gas production in the stools of patients on diets of butter soup and lactic acid milk was minimum, and in those of patients fed on breast-milk or in patients having chronic intestinal indigestion was maximum, while in normal stools of older children it was medium. Stools of chronic intes-

TABLE 1.—*Average Gas Production on Various Diets*

| | Dextrose, per Cent. | Lactose, per Cent. | Saccharose, per Cent. |
|---|---|---|---|
| Butter soup | 10 | 9 | 15 |
| Lactic acid milk | 10 | 10 | 12 |
| Soft diet, older children | 20 | 19 | 30 |
| Breast milk | 30 | 25 | 49 |
| Chronic intestinal indigestion | 48 | 46 | 40 |

tinal indigestion produced the largest amount of gas, notwithstanding the fact that many of these patients were on a lactic acid milk feeding, which normally produces a small amount of gas. Thus from the fermentation tubes alone it was suggested that Herter's findings might be substantiated.

Altogether, we have examined forty-one stools from cases of chronic intestinal indigestion—thirty-one of these were from thirteen undoubted cases, and ten were from nine questionable cases.

The microscopic examination of the smears of stools and fermentation culture tubes have also confirmed some of Herter's findings.

It is quite true that we have rarely found a stool smear that is strictly gram-positive; yet the picture as usually seen shows far more gram-positive bacilli than are commonly seen in normal stools. The feeding of lactic acid or protein milk to these children has altered the picture considerably, as we have found repeatedly that the stool smear changes materially within three to four days after the beginning of this type of feeding. The *Streptococcus lacticus* predominates, not only in the direct smear, but also in the cultures of the stool.

Thus to a certain extent we have confirmed the findings reported by Herter. That is to say, in chronic intestinal indigestion the change from gram-positive flora of infancy to gram-negative flora of older children has not taken place normally. Thus stools of these patients show a much larger proportion of gram-positive organisms both on direct smear and on culture than do those from normal children. Further than this we have been unable to accept Herter's findings. He claims to have subdivided these gram-positive bacilli into two distinct varieties, namely, *Bacillus bifidus* and *Bacillus infantilis,* the latter being a newly described variety which is practically always present in this type of patient. We will discuss this later.

Many of the organisms seen in infants' and in children's stools, including those of chronic intestinal indigestion, have been isolated and studied in detail. These organisms may be classified as in Table 2.

TABLE 2.—*Organisms Found in Stools*

| | | |
|---|---|---|
| 1. B. coli group | | |
| a. B. coli communis | | |
| b. B. coli communior | | |
| c. B. acidi lactici | | |
| d. B. lactis aerogenes | | |
| 2. Streptococcus lacticus. | Synonyms: | Micrococcus ovalis |
| | | Streptococcus duodenalis |
| | | Enterococcus |
| 3. Spore bearing group. (Not destroyed by heating at 80 C. for 10 minutes) Bacillus subtilis, B. megatherium, B. flexus, B. badius, etc. | | |
| 4. Aciduric group. Bacillus "A." | Synonyms: | B. bifidus |
| | | B. acidophilus |
| | | B. infantilis |

1. *B. Coli Group.*—These have been subdivided according to their various sugar reactions into classes suggested by Levine.[4] All members of this group produce acid and gas on dextrose and lactose. Two sugars, saccharose and dulcite, are used to differentiate them further into four groups. Types of each of these groups have been isolated, and their various reactions on milk have been studied chemically. They are all gram-negative short bacilli, and are more or less constant inhabitants of stools. Some form is present in all stools examined, even in those in which the gram-positive organisms are almost in pure culture. These organisms never become gram-positive, are easily isolated and cultured, and on the plates made directly from the stool emulsion, either aerobically or anaerobically, overgrow all other organisms. They form the largest group of organisms in the stool of the older child, and are present in much smaller numbers in the stool of the breast fed or the artificially fed infant. The various spore forms and *Streptococcus lacticus* are the only other organisms which can compare with them in viability. In the stools of chronic intestinal cases they are less common than normally.

4. Levine, Iowa State Coll. of Agric. and Mech. Arts, Bull. 62.

2. *Gram Positive Diplococci* (*Streptococcus lacticus*).—Only one group of organisms of this type has been isolated. Possibly on more detailed examination one could subdivide this group. This is the organism used in the preparation of lactic acid and protein milk in this hospital, and while appearing in much larger numbers in the stools of infants fed on these preparations, yet it is also present in fairly large numbers in other stools, that is, in those of the breast or artificially fed infant, and in those of older children. Its normal habitat is said to be the duodenum, in which region it overgrows other forms, and in turn is replaced by the colon organisms lower down the intestinal tract. This organism is typically gram-positive, and only loses the stain when it is languishing. At this time one element may be stained positive and the other one negative. It is easily isolated, and grows fairly luxuriantly on most mediums. It does not produce gas on sugars, and coagulates milk into a soft, flocculent curd. It is present in greatest abundance in the stools of infants fed on lactic acid and protein milk, and would seem to be preferable to *B. bulgaricus* or *B. acidophilus* so frequently used in adults to replace the colon flora. In three or four days after the beginning of its use, the stool smear changes from a gram-negative to a gram-positive type.

3. *Spore-bearing Group.*—Five or six varieties of spore forms have been isolated and cultured, and most of them have been identified. These are all gram-positive bacilli, and are quite easily isolated.

It is interesting to note that one spore, which resembles in many respects *Bacillus flexus,*[5] and which was the only one studied that produced ammonia in appreciable quantities from milk, has been isolated from two cases of chronic intestinal indigestion. The connection between this organism and the chronic intestinal condition, when the ammonia content of the stool is frequently quite high, is interesting and is still under investigation.

4. *Aciduric Group.*—This group of organisms has become of great interest to us. The question which we have not as yet satisfactorily answered is whether there are several distinct organisms in this group or whether it is a single organism, but extremely pleomorphic. As before-mentioned, Herter subdivides this group into two forms, *B. bifidus* and *B. infantilis.* Kendall [6] also divides it into two groups, namely, *Bacillus bifidus* and *Bacillus acidophilus,* while Noguchi [7] considers that all these various forms are in reality one organism, namely, *Bacillus bifidus;* he claims he can change from one to another by varying the mediums and conditions of growth. At the present time we

5. Bachelor, M. D.: J. Bacteriol. **4**:23, 1919.
6. Kendall, A. I.: Bacteriology, Philadelphia, Lea & Febiger, 1916.
7. Noguchi, H.: J. Exper. Med. **12**:182, 1910.

have not been able to demonstrate more than one organism, which is pleomorphic, at times entirely gram-negative, at other times gram-negative with gram-positive granules, and at other times entirely gram-positive. Under some conditions this organism will produce spores, under others it will not. Some forms coagulate milk, and others do not. It will grow aerobically or anaerobically, and will grow in mediums too acid for other organisms. At no time has the so frequently described field of bifid organisms been seen. In the breast milk stool, in which *Bacillus bifidus* is said to be very common, we find the most common organism to be a fine, slightly curved bacillus, usually gram-negative, but frequently with dark staining granules at either

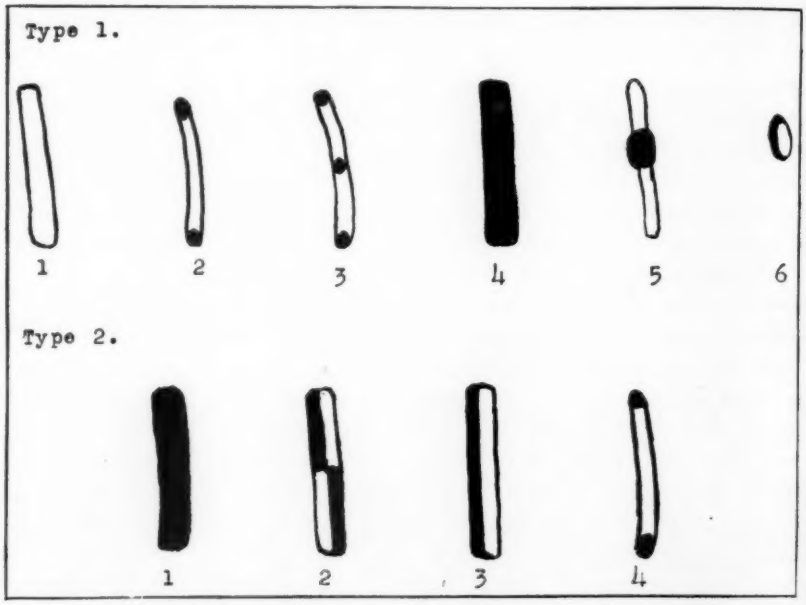


Chart 1.—Forms of aciduric bacteria ("Bacillus A") found in stools.

end. This we suspect to be *Bacillus bifidus,* but as bifid forms have never been seen we have not this outstanding characteristic to aid us in identifying this organism. We are attempting to subdivide these gram-positive bacilli by cultural and serologic reactions, but so far have not been able to obtain any clear cut distinction. In the meantime we are including all these forms under the term "Bacillus A." As mentioned in the foregoing, morphologically they can be changed from one form to another. The most common types are seen in Chart 1.

Many of the organisms of these various groups have been inoculated into different forms of milk mediums, and their products of metabolism estimated chemically by the Chemical Research Laboratories.

In summarizing the results which have been obtained there are a few points which stand out preeminently.

1. In its principal point we have confirmed the work of Herter, namely, that in chronic intestinal indigestion there is a delay in the normal change from the gram-positive, or aciduric group, to the gram-negative, or colon group.

2. We have not confirmed Herter's isolation of *Bacillus infantilis* as a separate entity, but tend rather to Noguchi's findings of a single pleomorphic organism.

3. *Streptococcus lacticus* is a very suitable organism for implanting in the intestinal tract, and will usually become the predominant organism in three or four days. This may be a valuable suggestion for adult therapy.

## CHEMICAL STUDIES ON FECES

In a preceding paper [1] on chronic intestinal indigestion, it was shown that in this disease there is an abnormally large loss through the feces of important food constituents, namely, fat, nitrogen, calcium and phosphorus, which is directly connected with the bulkiness of the feces and the high percentage of fat. Aside from indicating poor absorption and abnormal excretion, these studies of retention give little information regarding the intestinal conditions. It was hoped that some studies of ammonia and acid content of the feces might be more enlightening through affording evidence of abnormal fermentative or putrefactive activities. All determinations were made in emulsions of the fresh feces and a sample of the same was dried to constant weight to serve as a basis for calculation. Ammonia was determined by the Van Slyke modification of the Folin aeration method. Hydrogen ion concentration was estimated by Tisdall [8] according to his method for determining the $p_H$ of stools. Titratable acidity was obtained, using phenolphthalein as indicator. Organic acids, free and combined together, were determined by the use of the Van Slyke method for urine; and volatile acids, free and combined together, by acidifying the sample to Congo-red with phosphoric acid, distillation with steam, and titration of the distillate. The difference between the last two values should give approximately that for lactic acid, free and combined. Tables 4 and 5 give some results of this study, and Table 3, for comparison, some results obtained by other workers. As neither the volatile nor the nonvolatile acid values showed any apparent relation to the condition of the children or to variations in the diet, they have not been included in the tables. Table 3 is chiefly interesting in showing the close agreement between the two sets of results and in the finding of a

8. Tisdall, F. F., and Brown, A.: Am. J. Dis. Child. **27**:312, 1924.

TABLE 3.—*Results Obtained by Other Workers*

| Group | Number of Samples | Food | Ammonia Nitrogen, Average Mg. per Gm. Solids | Ammonia Nitrogen, per Cent. of Total Nitrogen |
|---|---|---|---|---|
| [Gamble, Am. J. Dis. Child. 9 : 519, 1915] | | | | |
| Infants not actually ill..... | 37 | Various; protein content 1.9 to 8.6 gm. per kg. | 4.2 | 9.0 |
| Those of group with highest ammonia | 10 | ..... | 6.8 | ... |
| Those of group with lowest ammonia | 10 | ..... | 2.3 | ... |
| Infants distinctly ill (not included above) | 4 | Buttermilk, protein milk, milk dilutions | 13.3 | 18.9 |
| [Van Slyke et al.[9]] | | | | |
| Convalescent infants, none acutely ill; 1-25 months | 57 | Breast milk, milk dilutions, protein milk, soft and mixed diets | 5.0 | 9.6 |
| Breast-fed from preceding group | 4 | Breast milk | 3.0 | 5.6 |
| Those of group with mucus in stools | 19 | Mostly milk dilutions | 6.7 | 10.8 |
| Those of group with highest ammonia in stools, all stools abnormal | 8 | Protein milk, milk dilutions | 13.7 | 22.3 |

TABLE 4.—*Ammonia Content and Acidity of Feces, Miscellaneous*

| Group | Number of Samples | Food | Ammonia Nitrogen, Average Mg. per Gm. Solids | Ammonia Nitrogen, per Cent. of Total Nitrogen | $p_H$ | Titratable Acidity C.c. N/10 NaOH per Gm. Solids |
|---|---|---|---|---|---|---|
| Normal infants..... | 4 | Breast milk | 2.7 | 7.4 | 5-6 | 15.1 |
| Convalescent infants..... | 5 | Butter-soup | 4.0 | 9.5 | 5-6 | 6.6 |
| Infant, atresia of bile duct.... | 1 | Breast milk, butter-soup | 1.7 | 7.8 | 5.8 | 16.1 |
| Practically normal infant, about 1 year | 1 | Milk only | 2.6 | 6.4 | 8 | 0 |
| Practically normal infant, about 1 year | 1 | Lactic acid milk and dextri-maltose | 2.1 | 6.5 | 7 | 1.0 |
| Normal infant, about 10 months | 4 | 4% lactic acid milk and dextri-maltose for months | 3.0 | 6.1 | 7-8 | 0.3 |
| Convalescent infants, no diarrhea | 13 | Various | 3.2 | ... | All but 2 7-8 | ... |
| Convalescent infants, no diarrhea | 7 | Lactic acid milk and 12-16% sugar | 3.3 | ... | All but 1 7-8 | ... |
| Girl, arthritis, 10 years..... | 1 | Lactic acid milk and fruit | 1.1 | 2.7 | 7 | 0.9 |
| Convalescents, not gastro-intestinal, 6-10 years | 3 | Mixed diet, including meat | 6.1 | 8.8 | 7 | 2.4 |
| Convalescents, not gastro-intestinal, 10-13 years | 2 | High protein diet with lactic acid milk | 5.1 | ... | ... | 0.9 |
| Epileptic boy, 13 years..... | 1 | High fat, low protein and carbohydrate diet | 3.6 | 6.6 | ... | 1.8 |
| Girl, infantilism, not intestinal, 6 years | 1 | Mixed diet | 3.4 | ... | ... | 3.2 |
| Recovered chronic intestinal indigestion, 7 years | 1 | Mixed diet, including milk | 4.5 | ... | ... | 1.8 |
| Recovered chronic intestinal indigestion, 8 years | 1 | High protein diet | 5.3 | 11.0 | 6.9 | 2.0 |
| Girl, active rickets..... | 1 | Soft diet | 9.3 | 15.3 | 6.8 | 3.3 |

large increase in ammonia content of the stools when the children were ill or the stools were abnormal. In the variety of conditions shown in Table 4, there is only one case in which the ammonia content of the feces is high, namely, that of a girl with active rickets. Table 5, which gives the values for the cases of chronic intestinal indigestion, shows that there is a consistently high ammonia content of the feces in this condition. The average for the mild cases is greater than any of the values in Table 4, except that for the rachitic girl, while that for the severe cases is much higher. Some of the findings in the individual cases are included in Table 5, which show that some of the children with chronic intestinal indigestion had as great an ammonia content of

TABLE 5.—*Ammonia Content and Acidity of Feces, Chronic Intestinal Indigestion*

| Group | Number of Samples | Food | Ammonia Nitrogen, Average Mg. per Gm. Solids | Ammonia Nitrogen, per Cent. of Total Nitrogen | $p_H$ | Titratable Acidity C.c. N/10 NaOH per Gm. Solids |
|---|---|---|---|---|---|---|
| Mild cases, some doubtful infantilism, 1-7 years | 9 | Mixed diet, lactic acid milk, rather high protein diet | 6.0 | 12.2 | 6.6-7.4 | 1.9 |
| Typical cases, including some severe ones, 2-9 years | 36 13 cases | Mixed diet, lactic acid milk, high protein diet | 8.2 | 17.0 | 6.7-8.0 (one 5.6) | 2.6 |
| Individual cases from preceding group: | | | | | | |
| Fl., 3 years, moderately severe | 3 | Mixed diet..... | 10.1 | 17.0 | ... | 1.7 |
| H. B., 2 years, severe..... | 2 | Soft and mixed diets | 9.1 | 24.7 | ... | 6 3 |
| McA., 3 years, moderately severe | 4 | High protein diet just begun | 6.2 | 12.3 | 7 | 2.0 |
| O'C., 8 years, improving... | 2 | Rather high protein diet | 5.7 | 10.9 | 7.6 | 3.1 |
| H., 5 years, very severe.... | 7 | High protein diet just begun | 10.1 | 17.9 | 7 | 2.4 |
| M., 6 years, moderately severe | 1 | Mixed diet for week previous | 5.6 | 11.4 | 5.6 | 8.4 |
| Same as preceding..... | 1 | High protein diet | 11.6 | 22.4 | ... | 6.5 |
| W., 5 years, severe..... | 3 | Soft diet, mostly bread and milk | 3.2 | 12.3 | 6.8 | 3.4 |
| Same as preceding..... | 4 | High protein diet | 9.8 | 21.4 | 7.3 | 2.3 |

the feces when on a diet containing a large proportion of carbohydrate as others not less severely ill when on a high protein diet. On the other hand, two showed a large increase in ammonia in the periods in which they were on high protein diet over that in the periods in which they were on mixed diet containing considerable carbohydrate. The acidity values included in Tables 4 and 5 are interesting, because they show a relation between the acidity of the feces and the kind of food, but seem to have no significance as regards the condition of chronic intestinal indigestion. Thus, increased ammonia content in the condition was the only positive finding in this study of the feces. According to Van Slyke [9] the ammonia in the feces must be mainly of bacterial origin.

9. Van Slyke, D. D.; Courtney, A. M., and Fales, H. L.: Am. J. Dis. Child. **9**:533, 1915.

In the large series of infants observed in his study, the ammonia nitrogen in the feces was found to equal or to exceed the free amino-acid nitrogen. Studies on hydrolysis of proteins have shown that when animal proteins, including casein, are split by nonbacterial agents, the ammonia nitrogen is less than one-seventh of the free amino-acid nitrogen. The free amino-acid nitrogen in the feces when determined in the present work was always found to be low. As this abnormal ammonia content of the feces in chronic intestinal indigestion may thus reasonably be expected to bear some relation to the bacterial activities of the intestinal tract, it was thought worth while to investigate the ammonia-producing powers of certain bacteria commonly abundant in children's feces and particularly in those of chronic intestinal indigestion.

### CHEMICAL STUDIES IN MILK CULTURES

As milk is the chief source of protein in the food of children at the period when chronic intestinal indigestion is supposed to have its start, and as milk with its large content of protein might be supposed to afford a medium more resembling that found in the intestinal tract than meat broth, especially under conditions of abnormal digestion, milk was chosen as the medium to be used in the present work.

The same procedure was followed throughout the work. The milk, modified as desired, was distributed into test tubes of about 150 c.c. capacity, half filling the tubes. These were sterilized in an autoclave at 15 pounds for twenty minutes. After being cooled to room temperature they were inoculated by the bacteriologist with the various bacteria, 1 c.c. of lactose broth culture being used in each case. They were then incubated under uniform conditions. In the beginning, the same chemical estimations were made as described in connection with the studies on feces. Reference to the findings for volatile and nonvolatile acids will be made later. Tables 6, 7 and 8 give the results of this study as regards ammonia, $p_H$ and titratable acidity. The number with the name of the bacteria indicates the child from whose feces the organism was isolated. All the numbers belong to cases of chronic intestinal indigestion except Cases 90 and 118, who were breast-fed infants, and Case 113, the same child as in Case 90 after he had been changed to a mixed diet. It is seen in Table 6 that among these organisms only certain of the spore-bearing bacilli and the "Bacillus A," on some occasions, produce ammonia in milk in quantities significant for this work, except in milk to which excessive amounts of casec have been added. In milk enriched with casec, colon bacillus makes a large increase and *Streptococcus lacticus* a small increase in ammonia production, at the same time increasing greatly their titratable acidity. The various strains and even different cultures of the same strain of "Bacillus A" show great variation in both ammonia and acidity production.

TABLE 6.—*Maximum Ammonia Production Found in Milk Cultures of Certain Bacteria*

| Bacteria | Medium | No. of Days Incubated | Ammonia C.c. N/10 in 100 C.c. | $p_H$ | Titratable Acidity C.c. N/10 in 100 C.c. |
|---|---|---|---|---|---|
| None | Fat-free sterilized milk | .. | 5 | 6.6 | 18 |
| None | ½ milk | .. | 3 | 6.6 | 9 |
| B. coli communior | Fat-free milk | 10 | 4 | ... | 53 |
| B. coli communior | ½ milk with 5% lactose | 9 | 2 | 5.2 | 43 |
| B. coli communior | ½ milk with 2% casec | 7 | 1 | 5.8 | 57 |
| B. coli communior | ½ milk with 7.6% lactose | 9 | 5 | ... | 38 |
| B. coli communior | ½ milk with 6.6% casec | 9 | 46 | ... | 118 |
| B. lactis aerogenes | Fat-free milk | 9 | 3 | 5.4 | 62 |
| B. acidi lactici | Fat-free milk | 7 | 9 | 4.7 | 111 |
| B. acidi lactici | Fat-free milk (repeated) | 7 | 1 | ... | 55 |
| B. acidi lactici | ½ milk with 5% lactose | 7 | 2 | 5.2 | 38 |
| B. acidi lactici | ½ milk with 2% casec | 7 | 3 | 5.2 | 50 |
| Streptococcus lacticus | Fat-free milk | 3 | 5 | 4.8 | 86 |
| Streptococcus lacticus | ½ milk with 5% lactose | 7 | 2 | 4.5 | 48 |
| Streptococcus lacticus | ½ milk with 2% casec | 7 | 2 | 4.6 | 66 |
| Streptococcus lacticus | ½ milk with 7.6% lactose | 9 | 2 | ... | 36 |
| Streptococcus lacticus | ½ milk with 6.6% casec | 9 | 7 | ... | 131 |
| Streptococcus lacticus (dairy culture in milk) | Fat-free milk | 9 | 5 | ... | 197 |
| B. acidophilus | Fat-free milk | 7 | 2 | 5.6 | 57 |
| B. acidophilus | ½ milk with 5% lactose | 7 | 1 | 5.6 | 29 |
| B. acidophilus | ½ milk with 2% casec | 7 | 2 | 5.6 | 53 |
| Bacillus "A" 90 | Fat-free milk | 14 | 8 | 4.5 | 129 |
| Bacillus "A" 90 | ½ milk with 5% lactose | 6 | 4 | 3.8 | 96 |
| Bacillus "A" 90 | ½ milk with 2% casec | 7 | 3 | 4.8 | 54 |
| Bacillus "A" 90 | ½ milk with 7.6% lactose | 9 | 3 | ... | 60 |
| Bacillus "A" 90 | ½ milk with 6.6% casec | 9 | 13 | ... | 195 |
| Bacillus "A" 118 | ½ milk | 15 | 3 | ... | 97 |
| Bacillus "A" 110 | Fat-free milk | 8 | 7 | ... | 55 |
| Bacillus "A" 112 | Fat-free milk | 12 | 25 | 7.1 | 13 |
| Another culture of preceding | Fat-free milk | 14 | 8 | 4.6 | 115 |
| Bacillus "A" 124 | Fat-free milk | 14 | 5 | ... | 111 |
| Bacillus "A" 114 | Fat-free milk | 9 | 13 | 5.0 | 64 |
| Another culture of preceding | Fat-free milk | 15 | 6 | ... | 25 |
| Bacillus "A" 114 | ½ milk with 7.6% lactose | 9 | 2 | ... | 10 |
| Spore-bearing bacillus 110 | Fat-free milk | 7 | 6 | 4.8 | 98 |
| Spore-bearing bacillus $109^1$ | Fat-free milk | 7 | 3 | 4.8 | 87 |
| $109^2$ | Fat-free milk | 7 | 3 | 4.8 | 88 |
| Spore-bearing bacillus 91 | Fat-free milk | 8 | 3 | 4.6 | 86 |
| Spore-bearing bacillus $107^3$ | Fat-free milk | 8 | 4 | 4.6 | 77 |
| $107^3$ | Fat-free milk | 10 | 6 | ... | 26 |
| $107^2$ | Fat-free milk | 10 | 9 | ... | 37 |
| $107^1$ | Fat-free milk | 8 | 8 | 6.0 | 36 |
| $107^4$ | Fat-free milk | 8 | 13 | 6.4 | 33 |
| Spore-bearing bacillus 113 | Fat-free milk | 10 | 19 | ... | 26 |
| B. subtilis (not from feces) | Fat-free milk | 10 | 7 | ... | 31 |
| Spore-bearing bacillus 89 (typ.) | Fat-free milk | 8 | 26 | 6.0 | 42 |
| Fresh strain | Fat-free milk | 10 | 38 | ... | 30 |
| | ½ milk with 5% lactose | 9 | 18 | 5.8 | 45 |
| | ½ milk with 2% casec | 7 | 19 | 6.0 | 48 |
| | ½ milk with 7.6% lactose | 9 | 44 | ... | 34 |
| Same culture as preceding | ½ milk with 6.6% casec | 9 | 131 | ... | 55 |

TABLE 7.—*Variation in Ammonia Production in Milk by Different Cultures of Spore 89*

| Culture | Number Days Incubated | Ammonia, C.c. N/10 in 100 C.c. | Titratable Acidity, C.c. N/10 in 100 C.c. |
|---|---|---|---|
| Cultures of original strain at different times | 8 | 26 | 42($p_H$ 6.0) |
| | 10 | 18 | 57 |
| | 8 | 12 | 63 |
| | 7 | 9 | 133($p_H$ 4.4) |
| | 10 | 6 | 183 |
| New strain recently recovered from feces of white rat | 10 | 38 | 30 |
| Old strain recently grown on blood agar | 10 | 16 | 32 |
| Old strain grown on plain agar | 10 | 21 | 32 |
| Old strain grown on lactose agar | 10 | 9 | 32 |
| Old strain grown with Bacillus "A" 114 | 10 | 12 | 32 |
| Old strain grown with Streptococcus lacticus | 10 | 14 | 34 |

TABLE 8.—*Effect on Ammonia Production of Spore-Bearing Bacillus 89 in Milk Culture with Other Organisms and with Lactic Acid*

| Cultures | No. of Days Incubated | Ammonia C.c. N/10 in 100 C.c. | Titratable Acidity, C.c. N/10 in 100 C.c. | $p_H$ |
|---|---|---|---|---|
| Spore 89 | 7 | 26 | 33 | 6.8 |
| Fat-free milk with lactic acid | .. | 2 | 70 | 4.8 |
| Same acidified milk and Spore 89 | 7 | 3 | 78 | 4.6 |
| Spore 89 | 7 | 26 | 33 | 6.8 |
| Streptococcus lacticus | 2 | 2 | 67 | 5.0 |
| Streptococcus lacticus incubated 3 days, then Spore 89 | 7 | 3 | 83 | 5.0 |
| Streptococcus lacticus | 7 | 4 | 80 | 4.8 |
| Spore 89 | 9 | 23 | 44 | ... |
| Streptococcus lacticus (milk culture from dairy) | 9 | 5 | 197 | ... |
| Streptococcus lacticus and Spore 89 inoculated together | 9 | 6 | 219 | ... |
| Streptococcus lacticus (unsterilized) | 1 | 4 | 49 | 5.4 |
| Streptococcus lacticus incub. 1 day, then sterilized | 1 | 4 | 48 | 5.3 |
| Streptococcus lacticus incub. 1 day, then Spore 89 | 7 | 4 | 82 | 4.8 |
| Streptococcus lacticus incub. 1 day, ster.; then Spore 89 | 7 | 4 | 66 | 4.9 |
| Streptococcus lacticus incub. 1 day, then Bac. "A" 90 | 7 | 4 | 97 | 4.2 |
| Streptococcus lacticus incub. 1 day, ster., then Bac. "A" 90. | 7 | 4 | 86 | 4.4 |
| Streptococcus lacticus incub. 1 day, then B. coli | 7 | 3 | 70 | 4.9 |
| Streptococcus lacticus incub. 1 day, ster., then B. coli | 7 | 4 | 57 | 5.0 |
| Spore 89 | 8 | 24 | 87 | 5.2 |
| Bacillus "A" 90 | 4 | 6 | 88 | 4.5 |
| Bacillus "A" 90 incub. 4 days, then Spore 89 | 10 | 11 | 130 | 4.4 |
| Bacillus "A" 90 | 14 | 8 | 129 | 4.5 |
| Spore 89 | 8 | 12 | 63 | ... |
| Bacillus "A" 90 | 3 | 5 | 55 | ... |
| Bacillus "A" 90 incub. 3 days, then Spore 89 | 8 | 5 | 104 | ... |
| Bacillus "A" 90 | 11 | 4 | 77 | ... |
| Bacillus "A" 90 and Sport 89 inoc. together | 8 | 6 | 107 | ... |
| Bacillus "A" 90 | 8 | 5 | 75 | ... |
| Spore 89 | 10 | 38 | 30 | ... |
| Bacillus "A" 124 | 4 | 6 | 86 | ... |
| Bacillus "A" 124 incub. 4 days, then Spore 89 | 10 | 5 | 104 | ... |
| Bacillus "A" 124 | 14 | 5 | 111 | ... |
| Spore 89 | 8 | 9 | 127 | 4.4 |
| Bacillus "A" 110 | 4 | 4 | 36 | 5.9 |
| Bacillus "A" 110 incub. 4 days, then Spore 89 | 9 | 5 | 95 | 4.4 |
| Bacillus "A" 110 | 12 | 6 | 88 | 4.6 |
| Spore 89 | 8 | 12 | 63 | ... |
| Bacillus "A" 110 | 3 | 5 | 38 | ... |
| Bacillus "A" 110 incub. 3 days, then Spore 89 | 8 | 5 | 83 | ... |
| Bacillus "A" 110 | 11 | 4 | 63 | ... |
| Bacillus "A" 110 and Spore 89 inoc. together | 8 | 5 | 107 | ... |
| Bacillus "A" 110 | 8 | 7 | 55 | ... |
| Spore 89 | 10 | 24 | 60 | ... |
| Bacillus "A" 110 | 9 | 5 | 26 | ... |
| Bacillus "A" 110 incub. 9 days, then Spore 89 | 5 | 5 | 50 | ... |
| Spore 89 | 8 | 24 | 87 | 5.2 |
| Bacillus "A" 110 | 4 | 6 | 48 | 5.4 |
| Bacillus "A" 110 incub. 4 days, then Spore 89 | 10 | 7 | 107 | 4.5 |
| Bacillus "A" 110 | 14 | 7 | 79 | 4.6 |
| Spore 89 | 8 | 9 | 127 | 4.4 |
| Bacillus "A" 112 | 4 | 6 | 22 | 6.4 |
| Bacillus "A" 112 incub. 4 days, then Spore 89 | 9 | 6 | 109 | 4.4 |
| Bacillus "A" 112 | 12 | 25 | 13 | 7.1 |
| Spore 89 | 8 | 24 | 87 | 5.2 |
| Bacillus "A" 112 | 4 | 7 | 42 | 5.4 |
| Bacillus "A" 112 incub. 4 days, then Spore 89 | 10 | 11 | 115 | 4.4 |
| Bacillus "A" 112 | 14 | 8 | 115 | 4.6 |
| Spore 89 | 10 | 6 | 183 | ... |
| Bacillus "A" 114 | 5 | 5 | 18 | ... |
| Bacillus "A" 114 incub. 5 days, then Spore 89 | 10 | 16 | 62 | ... |
| Bacillus "A" 114 | 15 | 6 | 25 | ... |
| Bacillus "A" 114 and Spore 89 inoc. together | 10 | 6 | 67 | ... |
| Spore 89 | 7 | 9 | 139 | 4.4 |
| Bacillus "A" 114 | 4 | 5 | 52 | 5.3 |
| Bacillus "A" 114 incub. 4 days, then Sport 89 | 5 | 8 | 75 | 5.0 |
| Bacillus "A" 114 incub. 4 days, then Spore 89 | 9 | 7 | 93 | 4.6 |
| Bacillus "A" 114 | 9 | 13 | 64 | 5.0 |
| Bacillus "A" 114 | 13 | 8 | 85 | 4.6 |
| Spore 89 | 10 | 18 | 57 | ... |
| Bacillus "A" 114 | 5 | 2 | 16 | ... |
| Bacillus "A" 114 incub. 5 days, then Spore 89 | 10 | 8 | 72 | ... |
| Bacillus "A" 114 | 15 | 5 | 37 | ... |

Certain of the spore-bearing bacilli isolated from the feces always show some ammonia production, while others show none. As the spore-bearing bacillus from Case 89 was always an ammonia producer and as first observed a very active one, attention was concentrated on this organism. Chart 2 gives the curves of ammonia production by Spore 89, in what is considered its characteristic condition, when grown in plain milk, in half milk with lactose addition and in diluted milk with casec addition. Before going on to the further consideration of the ammonia and acid forming powers of this Spore 89, as shown in Tables 7 and 8, attention is called to Charts 3 and 4, showing the curves of hydrogen ion concentration and titratable acidity respectively in plain milk cultures from

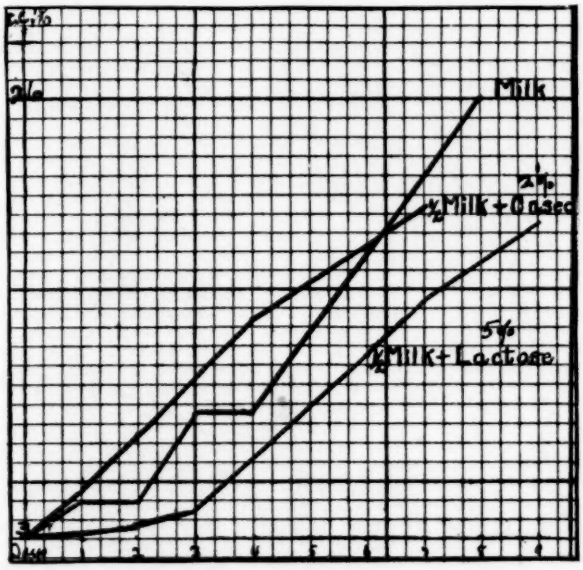


Chart 2.—Ammonia in milk cultures, Spore 89.

day to day of four of the organisms studied. Colon bacillus and *Streptococcus lacticus* produce their acidity more quickly than "Bacillus A" forms, but do not reach so high a degree of acidity as some "Bacillus A" strains, particularly those from the stools of breast-fed infants. Some cultures of "Bacillus A" have shown an acidity still increasing at the end of the twelfth day. The forms of "Bacillus A" obtained from the chronic intestinal indigestion stools almost always developed their acidity more slowly than those from the stools of breast fed infants, and commonly showed no coagulation at the end of the fourth day's incubation. Chart 5 gives the curve of titratable acidity of Spore 89 in three different phases of its ammonia and acidity producing activity. The middle line, the same as that in Chart 4, represents what seems to be the most charac-

teristic condition; the lower line represents a strain with a maximum ammonia and minimum acidity producing activity, just recovered from the feces of a white rat after it had been fed cultures of Spore 89; while the upper line represents the organism after a long series of transfers on plain agar, when the ammonia producing power was practically lost and the acidity production was at its maximum.

The first part of Table 7 needs little comment. It is readily seen that the increase in titratable acidity when there is a decrease in ammonia-producing power is not due to the lessened requirement for neutralizing ammonia, since the acidity increase is entirely out of proportion to the

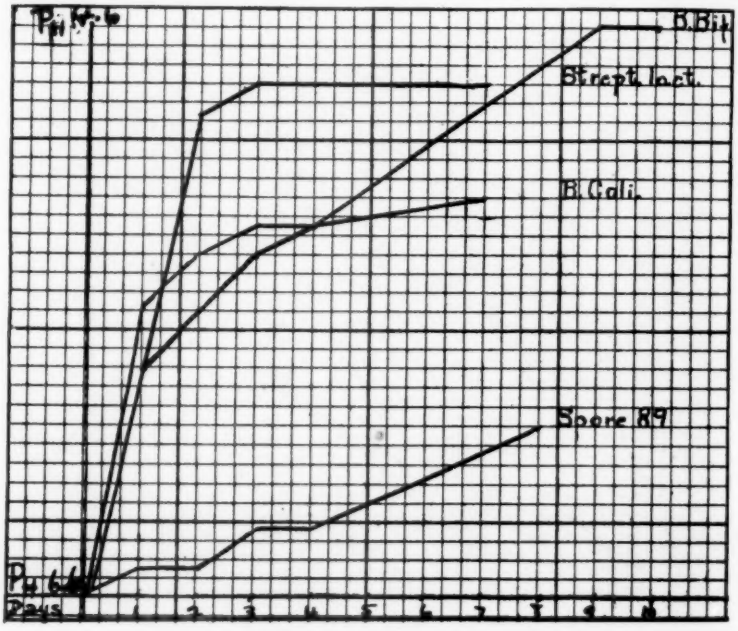


Chart 3.—Hydrogen ion concentration in milk.

ammonia decrease. In the last part are given the ammonia and titratable acidity of some plain milk cultures of Spore 89 after it had been grown for a time under varying conditions, in the hope of learning something concerning the cause of its change in character. The results are inconclusive, though the contrast between the ammonia production in the culture from the plain agar and in that from the lactose agar is suggestive. The period of growth allowed under the various conditions was probably too short to cause much differentiation.

Table 8 gives the results of an investigation into the effect on ammonia production in milk of growing Spore 89 with the acid-producing organisms and in milk acidified with lactic acid. It is seen

that the ammonia production of Spore 89 in milk is always entirely inhibited or greatly reduced when this bacillus is incubated in conjunction with an acid-producing organism or in acidified milk. An apparent exception appears in the first group with "Bacillus A" 114, when 16 c.c. of decinormal ammonia was produced in the culture in which "Bacillus A" was incubated alone for five days and then ten days longer after the inoculation with Spore 89. It happened in this case that the spore form was in the phase producing the least ammonia and most acid. It looks here as if the increased ammonia production were to be attributed to "Bacillus A" 114 instead of to the spore form. Here, then, is another instance of the irregularity of behavior of "Bacillus A" forms.

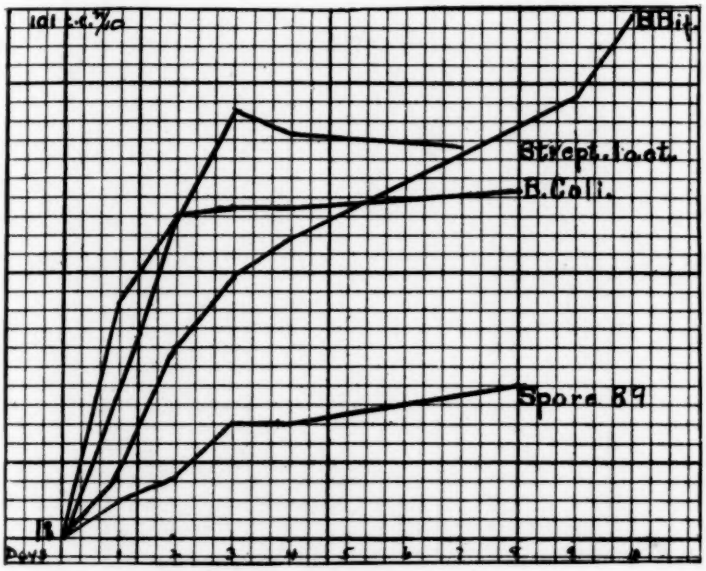


Chart 4.—Titration acidity in milk.

That the spore-bearing bacillus in conjunction with the acid-producing organisms, or in sterile acid mediums, is not entirely inactive is indicated by the acidity values. Very frequently the acidity reached by the two organisms together is considerably greater than that attained by the acid producer alone in the same period of time, and in sterilized *Streptococcus lacticus* culture and in acidified milk, incubation with the spore form carried the acidity further. On the other hand, in one or two instances there was either no increase or a slight decrease in acidity from incubating the spore with one of "Bacillus A" forms. In these instances there happened to be the combination of a strongly acid producing "Bacillus A" form with a strongly ammonia producing stage of the spore form.

These organisms were further studied in respect to their activity in breaking down protein and sugar in milk.

### METHODS

The incubated milk samples were well shaken, and if necessary were ground in a mortar to bring them to a homogeneous emulsion before the portions were measured out for analysis. The method used for the sugar estimations is based on Fehling's gravimetric process. The proteins of the milk were precipitated by copper sulphate and sodium hydroxid according to Soxhlet's method.[10] The reduction was accom-

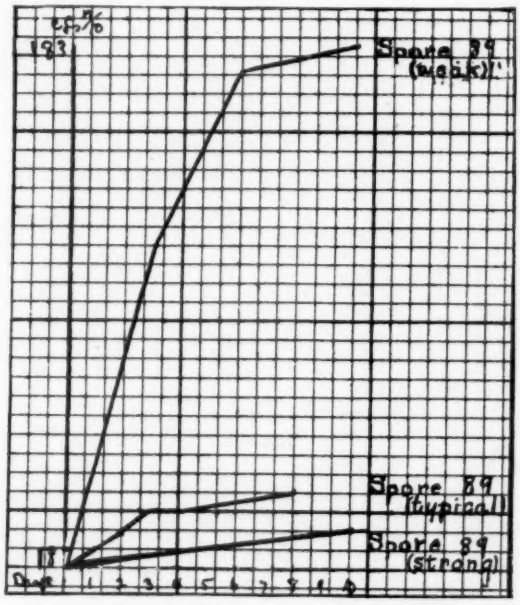


Chart 5.—Titration acidity in milk.

plished by heating in boiling water as suggested in the Defren-O'Sullivan [11] procedure. The cuprous oxid was washed, dried and weighed directly and the sugar calculated from Munson and Walker's table.

Protein breakdown was investigated by estimating the total nonprotein nitrogen and its approximate distribution into the proteose-peptone, amino-acid, ammonia and unknown rest fractions. This was carried out according to the following scheme. 1. Nonprotein nitrogen was determined in the filtrate by the Kjeldahl-Gunning total nitrogen method (as were all nitrogen contents of filtrates throughout the proce-

10. Leach, A. E.: Food and Inspection Analysis, Ed. 3, New York, John Wiley & Sons, 1914, p. 150.

11. Defren-O'Sullivan: Footnote 10, p. 594.

TABLE 9.—*Nitrogen Distribution and Use of Sugar in Milk Cultures of Various Bacteria in 100 c.c.*

| Cultures | Total Nonprotein Nitrogen | | Nitrogen of Proteoses and Peptones | | Total Amino-Acid Nitrogen | | Ammonia Nitrogen | | Nitrogen of Unknown Rest | | Grams of Sugar Used | Per Cent. of Total Sugar | Titratable Acidity, C.c. N/10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | | | |
| Average 8 samples uninoculated fat-free sterilized milk | 48 | 13.0 | 20 | 5.4 | 21 | 5.7 | 5 | 1.3 | 2 | 0.5 | .... | .... | .. |
| Fat-free milk acidified with lactic acid, incub. 10 days | 60 | 17.5 | 34 | 9.9 | 23 | 6.7 | 3 | 0.9 | 0 | 0.0 | 0.13 | 2.8 | 59 |
| Fat-free milk inoculated with Strept. lacticus, incub. 10 days | 76 | 20.3 | 25 | 6.7 | 46 | 12.3 | 5 | 1.3 | 0 | 0.0 | 1.64 | 35 6 | 197 |
| Fat-free milk inoculated with B. coli communior, incub. 10 days | 43 | 11.9 | 24 | 6.6 | 10 | 2.8 | 4 | 1.1 | 5 | 1.4 | 0.44 | 9.5 | 53 |
| Fat-free milk inoculated with Bac. "A" 90 | | | | | | | | | | | | | |
| Incubated 3 days | 48 | 13.5 | 15 | 4.2 | 27 | 7.6 | 5 | 1.4 | 1 | 0.3 | 0.10 | 2.2 | 55 |
| Incubated 8 days | 47 | 13.4 | 17 | 4.8 | 25 | 7.2 | 5 | 1.4 | 0 | 0 0 | 1.00 | 22.4 | 75 |
| Incubated 11 days | 55 | 15.1 | 25 | 6.9 | 19 | 5.2 | 4 | 1.1 | 7 | 1.9 | 0.36 | 8.1 | 77 |
| ½ milk inoculated with Bac. "A" 118 | | | | | | | | | | | | | |
| Incubated 5 days | 46 | 23.6* | 20 | 10.3* | 24 | 12.3* | 2 | 1.0* | 0 | 0.0 | 0.80 | 34.8* | 93 |
| Incubated 15 days | 58 | 30.4 | 23 | 12.1 | 32 | 16.8 | 3 | 1.5 | 0 | 0.0 | 0.77 | 33.5 | 97 |
| Fat-free milk inoculated with Bac. "A" 110 | | | | | | | | | | | | | |
| Incubated 3 days | 56 | 15.9 | 27 | 7.7 | 23 | 6.5 | 5 | 1.4 | 1 | 0.3 | 0.26 | 5.8 | 38 |
| Incubated 8 days | 53 | 15.0 | 24 | 6.8 | 22 | 6.2 | 7 | 2.0 | 0 | 0.0 | 0.47 | 10.5 | 55 |
| Incubated 11 days | 48 | 14.6 | 20 | 6.1 | 17 | 5.2 | 4 | 1.2 | 7 | 2.1 | 1.16 | 26.0 | 63 |
| Another culture, incubated 9 days | 48 | 13.6 | 19 | 5.4 | 24 | 6.8 | 5 | 1.4 | 0 | 0.0 | .... | .... | .. |
| Fat-free milk inoculated with Bac. "A" 124 | | | | | | | | | | | | | |
| Incubated 4 days | 45 | 13.1 | 4 | 1.2 | 35 | 10.2 | 6 | 1.7 | 0 | 0.0 | 0.89 | 19.3 | 86 |
| Incubated 14 days | 58 | 15.8 | 25 | 6.8 | 28 | 7.6 | 5 | 1.4 | 0 | 0.0 | 1.24 | 26.8 | 111 |
| Fat-free milk inoculated with Bac. "A" 114 | | | | | | | | | | | | | |
| Incubated 5 days | 55 | 14.7 | 22 | 5.9 | 22 | 5.9 | 5 | 1.3 | 6 | 1.6 | —0.03 | —0.7 | 18 |
| Incubated 15 days | 54 | 14.4 | 8 | 2.1 | 35 | 9.4 | 6 | 1.6 | 5 | 1.3 | 0.19 | 4.3 | 25 |
| Another culture, incubated 5 days | 40 | 10.8 | 15 | 4.0 | 19 | 5.2 | 2 | 0.5 | 4 | 1.1 | 0.09 | 2.0 | 16 |
| Another culture, incubated 15 days | 41 | 11.2 | 2 | 0.5 | 34 | 9.3 | 5 | 1.4 | 0 | 0.0 | 0.04 | 0.9 | 37 |

* T. N. and sugar reduced one-half.

dure), after the removal of the protein by acidifying with dilute acetic acid and boiling. The amount of acid to be used had to be varied according to the degree of coagulation and hydrolysis of the milk. 2. In a second sample of the original culture, the tannic acid precipitation method of Van Slyke [12] was used for removal of proteoses and peptones as well as protein, and the total nitrogen of this filtrate gave the nitrogen of the amidocompounds and ammonia and any other end-products of proteolysis. The difference between the nitrogen in filtrates 1 and 2 thus gave that of the proteose-peptone fraction. 3. In a third sample of the culture, precipitation with phosphotungstic acid (10 per cent. in 2 per cent. hydrochloric acid, Benedict method) was used to remove protein, proteoses and peptones, and in addition the basic amino-acids and supposedly ammonia. The total nitrogen in this filtrate should be that of the nonbasic amino-acids and presumably any nonamino nitrogenous compounds except ammonia.[13] In this filtrate was also estimated the amino-acids by the modification of the formol-titration method included in the A. O. A. C. Methods of Analysis. Any ammonia not removed by the phosphotungstic acid would be included in this value. The difference between the nitrogen in filtrates 2 and 3 should be that of the basic amino-acids, and the difference between the total nitrogen of filtrate 3 and that obtained by the amino-acid estimation should be the nitrogen of the unknown rest. Ammonia was always determined in a sample of the original culture. It happened that in our use of the phosphotungstic precipitation, ammonia was not always entirely removed, as shown by estimations of ammonia made in the filtrate, whenever material allowed. Investigation showed that the completeness of removal of ammonia depended on the excess of the phosphotungstic acid reagent and the length of time between its addition and filtration. As the error due to this irregularity affects the separate determination of basic and nonbasic amino-acids, only the sum of these two values is included in the tables.

Table 9 shows for the cultures of colon bacillus and "Bacillus A" little difference in nitrogen distribution from that in the uninoculated autoclaved milk. Streptococcus lacticus culture alone among the non-sporebearing organisms shows a definite increase in nonprotein nitrogen, mainly in the amino-acid fraction.

The findings for spore-bearing bacilli in Table 10 are very different. It should be noted that Spore 89 shows, in its strongly proteolytic state, the largest ammonia and unknown rest fractions found, and that in the different cultures of this organism these fractions vary closely with the total nonprotein nitrogen. The next to the last section of the table

12. Van Slyke, L. L.: New York Exp. Station Bull., 215, 102.
13. Van Slyke, D. D.: New York M. J., Aug. 10 and 17, 1912.

TABLE 10.—*Nitrogen Distribution and Use of Sugar in Milk Cultures of Various Spore-Bearing Bacilli in 100 c.c.*

| Cultures | Total Nonprotein Nitrogen | | Nitrogen of Proteoses and Peptones | | Total Amino-Acid Nitrogen | | Ammonia Nitrogen | | Nitrogen of Unknown Rest | | Grams of Sugar Used | Per Cent. of Total Sugar | Titratable Acidity, C.c. N/10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | | | |
| Fat-free milk inoculated with B. subtilis, incubated 10 days.. | 287 | 81.5 | 94 | 26.7 | 122 | 34.6 | 7 | 2.0 | 64 | 18.2 | —0.06 | —1.3 | 31 |
| Fat-free milk inoculated with Spore-Bearing Bacillus 113 | | | | | | | | | | | | | |
| Incubated 10 days | 314 | 82.2 | 110 | 28.8 | 93 | 24.3 | 19 | 5.0 | 92 | 24.1 | 0.18 | 3.9 | 26 |
| Fat-free milk inoculated with Spore-Bearing Bacillus | | | | | | | | | | | | | |
| $10^{7}$, incubated 10 days | 143 | 39.2 | 67 | 18.4 | 46 | 12.6 | 9 | 2.5 | 21 | 5.7 | 0.40 | 8.7 | 37 |
| $10^{8}$, incubated 10 days | 126 | 34.5 | 61 | 16.7 | 43 | 11.8 | 6 | 1.6 | 16 | 4.4 | 0.26 | 5.6 | 26 |
| Fat-free milk inoculated with Spore-Bearing Bacillus 89, | | | | | | | | | | | | | |
| recent strain from rat; incubated 10 days | 332 | 88.1 | 89 | 23.6 | 87 | 23.1 | 38 | 10.1 | 118 | 31.3 | 0.01 | 0.2 | 30 |
| Another culture of same, incubated 9 days | 300 | 76.2 | 0 | 0 | 167 | 42.4 | 23 | 5.8 | 110 | 28.0 | 0.09 | 2.0 | 44 |
| Fat-free milk inoculated with Spore-Bearing Bacillus 89, | | | | | | | | | | | | | |
| original strain; incubated 5 days | 278 | 77.2 | 75 | 20.8 | 88 | 24.4 | 14 | 3.9 | 101 | 28.1 | .... | .... | ... |
| Incubated 10 days | 279 | 75.6 | 34 | 9.2 | 109 | 29.5 | 24 | 6.5 | 112 | 30.4 | .... | .... | ... |
| Another culture, incubated 9 days | 234 | 62.9 | 0 | 0 | 148 | 39.8 | 18 | 4.8 | 68 | 18.3 | 0.44 | 9.6 | 57 |
| Another culture, incubated 8 days | 187 | 52.0 | 29 | 8.1 | 97 | 27.0 | 12 | 3.3 | 49 | 13.6 | 0.46 | 10.3 | 63 |
| One-half milk inoculated with old strain of Spore 89 | | | | | | | | | | | | | |
| Incubated 3 days | 88 | 47.1 | 31 | 16.6 | 50 | 26.8 | 4 | 2.1 | 3 | 1.6 | 0.62 | 27.0 | 75 |
| Incubated 6 days | 98 | 50.8 | 38 | 19.7 | 51 | 26.4 | 5 | 2.6 | 4 | 2.1 | 0.96 | 41.7 | 118 |
| Incubated 9 days | 98 | 52.1 | 34 | 18.1 | 55 | 29.3 | 5 | 2.6 | 4 | 2.1 | 1.04 | 45.2 | 124 |
| Same culture in fat-free milk | | | | | | | | | | | | | |
| Incubated 3 days | 85 | 24.7 | 40 | 11.6 | 35 | 10.2 | 5 | 1.4 | 5 | 1.5 | 1.31 | 29.7 | 120 |
| Incubated 6 days | 112 | 31.8 | 45 | 12.8 | 50 | 14.2 | 5 | 1.4 | 12 | 3.4 | 1.61 | 36.5 | 175 |
| Incubated 9 days | 117 | 34.0 | 32 | 9.3 | 74 | 21.5 | 6 | 1.7 | 5 | 1.5 | 1.67 | 37.9 | 183 |
| Same culture in 80 per cent. milk with 5 per cent. lactose | | | | | | | | | | | | | |
| Incubated 3 days | 58 | 19.8 | 25 | 8.5 | ... | .... | 4 | 1.3 | ... | .... | 0.44 | 6.3 | 105 |
| Incubated 6 days | 79 | 26.5 | 36 | 12.1 | 31 | 10.4 | 5 | 1.7 | 7 | 2.3 | 0.91 | 13.0 | 147 |
| Incubated 9 days | 79 | 28.1 | 33 | 11.7 | 38 | 13.5 | 5 | 1.8 | 3 | 1.1 | —0.16 | —2.3 | 151 |
| Fat-free milk inoculated with old strain of Spore 89 after | | | | | | | | | | | | | |
| being newly grown variously | | | | | | | | | | | | | |
| On blood agar, incubated 10 days | 237 | 66.0 | 47 | 13.1 | 102 | 28.4 | 16 | 4.5 | 72 | 20.0 | —0.10 | —2.2 | 32 |
| On plain agar, incubated 10 days | 218 | 62.1 | 51 | 14.5 | 94 | 26.8 | 21 | 6.0 | 52 | 14.8 | —0.05 | —1.1 | 32 |
| With strept. lact. on plain agar, incubated 10 days.... | 204 | 58.0 | 34 | 9.7 | 99 | 28.1 | 14 | 4.0 | 57 | 16.2 | 0.04 | 0.9 | 34 |
| With Bac. "A" 114 on plain agar, incubated 10 days.... | 200 | 56.0 | 48 | 13.4 | 95 | 26.6 | 12 | 3.4 | 45 | 12.6 | 0.04 | 0.9 | 32 |
| On 1 per cent. lactose agar, incubated 10 days | 188 | 53.6 | 39 | 11.1 | 94 | 26.8 | 9 | 2.6 | 46 | 13.1 | —0.04 | —0.9 | 32 |

gives the nitrogen distribution for this bacillus in the stage when it has lost its ammonia producing activity and has become a great acid producer. It is still proteolytic to some extent, but there is practically no ammonia to be found and usually but little of the unknown rest fraction.

The work reported in Table 11 was carried out mainly to learn whether or not there was any essential difference in the behavior of these organisms in broth from that in milk. Unfortunately, the non-amino determinations were lost through the use of too great an excess of the phosphotungstic acid reagent. The results obtained, however, are sufficient to serve the purpose. It is fairly evident that only the spore form carried the proteolysis beyond the amino-acid stage.

The results, as regards proteolysis, of culturing Spore 89 with the acid producing organisms and in acidified milk are given in Table 12. There seems to have been some effect from growing the spore with the other organism in every instance except possibly in the case of "Bacillus A" 124, the effect being shown in an increased amino-acid or unknown rest fraction or in the increase of both of these. "Bacillus A" 114 shows the most striking results from being grown with Spore 89. In the first observation, when "Bacillus A" 114 was grown with a weakly proteolytic culture of Spore 89, there was marked proteolysis. The amino-acid and unknown rest fractions were much increased when the two organisms were inoculated together, and there was a much greater increase in these fractions and also in ammonia when "Bacillus A" was inoculated five days ahead of Spore 89. In a second observation when the spore was in a more strongly proteolytic condition the results were similar, though this time the increase in ammonia was small. The first of these two observations certainly suggests either a symbiotic activity or else that one or both of the organisms has undergone a transformation. As a whole, the results shown in this table are difficult to explain, and show the need of more work being done.

Tables 9 to 12, inclusive, also show the use of sugar in comparison with the proteolytic activity of the organisms being studied. It is interesting to note in Table 9 that *Streptococcus lacticus,* which shows a certain degree of proteolysis, also makes a greater use of sugar in milk than the other acid producing organisms or colon bacillus. From the table for the spore-bearing bacilli it is noted that Spore 89 in its strongly proteolytic condition makes little use of sugar in milk, but when weakly proteolytic the use of sugar and the production of acidity is comparatively great. When *Streptococcus lacticus* and Spore 89 are grown together, with the increased proteolysis there is also seen to be increased use of sugar. When "Bacillus A" and Spore 89 are grown together, the use of sugar is approximately that of "Bacillus A" alone.

TABLE 11.—*Nitrogen Distribution and Use of Sugar in Broth Cultures of Various Bacteria in 100 c.c.*

TABLE 11.—*Nitrogen Distribution and Use of Sugar in Broth Cultures of Various Bacteria in 100 c.c.*

| Cultures | Total Nonprotein Nitrogen | | Nitrogen of Proteoses and Peptones | | Total Amino-Acid and Rest Nitrogen | | Ammonia Nitrogen | | Grams of Sugar Used | Per Cent. of Total Sugar | Titratable Acidity C.c. N/10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | | | |
| Uninoculated 1 per cent. lactose broth | 91 | 93.8 | 48 | 49.5 | 42 | 43.3 | 1 | 1.0 | .... | .... | 8 |
| 1 per cent broth inoculated with Streptococcus lacticus | 85 | 93.4 | 52 | 57.1 | 28 | 30.8 | 5 | 5.5 | 0.24 | 21.6 | 23 |
| 1 per cent. broth inoculated with B. coli communior | 87 | 93.6 | 53 | 57.0 | 33 | 35.5 | 1 | 1.1 | 0.17 | 15.3 | 14 |
| 1 per cent. broth inoculated with Bacillus "A" 90 | 80 | 86.0 | 23 | 24.7 | 54 | 58.1 | 3 | 3.2 | 0.17 | 15.3 | 20 |
| 1 per cent. broth inoculated Bacillus "A" 114 | 90 | 96.8 | 27 | 29.0 | 61 | 65.6 | 2 | 2.2 | 0.13 | 11.7 | 14 |
| 1 per cent. inoculated with Spore-Bearing Bacillus 89 | 87 | 91.6 | 0 | 0 | 57 | 60.0 | 31 | 32.6 | 0.30 | 27.0 | 8 |

TABLE 12.—*Nitrogen Distribution and Use of Sugar in Cultures of Spore 89 in Acidified Milk and in Plain Milk in Conjunction with Another Organism in 100 c.c.*

| Cultures | Total Nonprotein Nitrogen | | Nitrogen of Proteoses and Peptones | | Total Amino-Acid Nitrogen | | Ammonia Nitrogen | | Nitrogen of Unknown Rest | | Grams of Sugar Used | Per Cent. of Total Sugar | Titratable Acidity, C.c. N/10 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | | | |
| Fat-free milk acidified with lactic acid, inoculated with Spore 89, 10 days | 61 | 17.2 | 26 | 7.3 | 29 | 8.2 | 4 | 1.1 | 2 | 0.6 | 0.34 | 7.4 | 65 |
| Fat-free milk inoculated with streptococcus lacticus and Spore 89 together, incubated 10 days | 97 | 26.5 | 41 | 11.2 | 45 | 12.3 | 6 | 1.6 | 5 | 1.4 | 2.04 | 44.3 | 219 |
| Fat-free milk inoculated with Bac. "A" 90, incubated 3 days, then 8 days in conjunction with Spore 89 | 57 | 17.0 | 25 | 7.5 | 16 | 4.8 | 5 | 1.5 | 11 | 3.2 | 1.08 | 24.2 | 104 |
| Same cultures of Bac. "A" 90 and Spore 89 inoculated into fat-free milk and incubated 8 days; Spore 89 in weakly proteolytic phase | 74 | 22.1 | 20 | 6.0 | 45 | 13.5 | 6 | 1.8 | 3 | 0 8 | 1.08 | 24.2 | 107 |
| One-half milk inoculated with Bac. "A" 118, incubated 5 days, then 10 days in conjunction with Spore 89 | 57 | 30.0 | 19 | 10.0 | 24 | 12.6 | 4 | 2.1 | 10 | 5.3 | 0.82 | 35.7 | 102 |
| Same cultures of Bac. "A" 118 and Spore 89 inoculated into one-half milk and incubated 10 days; Spore 89 in very weakly proteolytic phase | 54 | 29.5 | 21 | 11.5 | 27 | 14.8 | 3 | 1.6 | 3 | 1.6 | 0 94 | 40.9 | 92 |
| Fat-free milk inoculated with Bac. "A" 124, incubated 4 days, then 10 days with Spore 89 | 62 | 17.4 | 27 | 7.6 | 30 | 8.4 | 5 | 1.4 | 0 | 0 | 1.21 | 26.2 | 104 |
| Fat-free milk inoculated with Bac. "A" 110, incubated 3 days, then 8 days with Spore 89 | 54 | 16.4 | 24 | 7.3 | 20 | 6.1 | 5 | 1.5 | 5 | 1.5 | 0.90 | 20.2 | 83 |
| Same cultures of Bac. "A" 110 and Spore 89 inoculated into fat-free milk and incubated 8 days; Spore 89 weakly prot. | 85 | 23.9 | 27 | 7.6 | 44 | 12.4 | 5 | 1.4 | 9 | 2.5 | 1.06 | 23.8 | 107 |
| Fat-free milk inoculated with Bac. "A" 110 (another culture), incubated 9 days, then 5 days with Spore 89 | 90 | 26.1 | 35 | 10.2 | 28 | 8.1 | 5 | 1.4 | 22 | 6.4 | .... | .... | ... |
| Fat-free milk inoculated with Bac. "A" 114, incubated 5 days, then 10 days with Spore 89 | 197 | 68.6 | 2 | 0.7 | 122 | 42.5 | 16 | 5.6 | 57 | 19.8 | 1.65 | 37.4 | 62 |
| Same cultures of Bac. "A" 114 and Spore 89 inoculated into fat-free milk and incubated 10 days; Spore 89 very weakly proteolytic | 100 | 29.2 | 15 | 4.4 | 51 | 14.9 | 6 | 1.8 | 28 | 8.1 | 0.90 | 20.4 | 67 |
| Fat-free milk inoculated with Bac. "A" 114 (another culture), incubated 5 days, then 10 days with Spore 89 | 151 | 40.3 | 1 | 0.3 | 98 | 26.2 | 8 | 2.1 | 44 | 11.7 | 0.55 | 12.0 | 72 |

except in the case of "Bacillus A" 114, when, with the greatly increased proteolysis there is a much greater use of sugar, and accompanying increase in titratable acidity.

Table 13 gives the effect on protein and sugar breakdown and acid production by the organisms when they are grown in diluted milk to which a large quantity of lactose had been added, and in diluted milk with the addition of a large amount of casec. In the medium low in protein and high in sugar, colon bacillus more than doubles its use of sugar and shows no proteolytic activity. Of "Bacillus A" forms, 114 made more use of sugar but produced less acidity, while 90, the form from the stool of a breast-fed infant, showed a slight proteolysis but used less sugar. The spore form 89, when the protein was cut in half and the sugar much increased, broke down actually half as much protein as in plain undiluted milk, at the same time producing more ammonia, but used a great deal more sugar without increasing the titratable acidity. In the medium in which the sugar is only half that of plain milk but the protein content is greatly increased by the addition of casec, proteolysis is increased in all the cultures. The increase is least in that of "Bacillus A" 114, most in those of colon bacillus and Spore 89, with a greatly increased ammonia production by these two, a lesser one by "Bacillus A" 90 and practically none by *Streptococcus lacticus*. In addition to its great protein breakdown, colon bacillus used up all the sugar present and "Bacillus A" 90 nearly all. Spore 89 used about the same amount of sugar as when it broke down a much smaller amount of protein, and *Streptococcus lacticus* used less sugar with the smaller supply but produced much greater acidity. "Bacillus A" 114 used very little sugar in the low sugar medium. In the high sugar series, plating the residues of the cultures showed the best growth from the 90 culture, a good growth from 89, less from 114 and *Streptococcus lacticus* and practically none from colon bacillus. The plates from the high protein cultures showed extremely heavy growth with all the residues except the spore form, and this gave a fair growth.

The latter part of Table 13 includes all the other results from the investigation of volatile and nonvolatile acid production by the organisms which seemed worth reporting. Much difficulty was experienced in applying the Van Slyke method for estimating organic acids to these milk cultures. Late in the work, it was found that the addition of a small quantity of hydrochloric acid to the samples before precipitation gave a clear filtrate, and the latest determinations are felt to be more reliable than the earlier ones. The bracketed columns were obtained by subtracting from the values in the column to the left the corresponding value for the control uninoculated milk, in order to bring out more clearly the effect due to the inoculation. It is seen that titratable acidity is not increased in any instance in the high sugar medium over that in

TABLE 13.—*Use of Protein and of Sugar and Acid Production in Lactose-enriched and in Casec-enriched Milk Cultures of Certain Bacteria, Incubated 10 Days, in 100 c.c.*

| Culture | Total Nonprotein Nitrogen | | Ammonia Nitrogen | | Grams of Sugar Used | Per Cent. of Total Sugar | Titratable Acidity, C.c. N/10 | Total Organic Acids, Free and Combined, C.c. N/10 | Volatile Acids, Free and Combined, C.c. N/10 | Non-Volatile (org.) Acids, Free and Combined, C.c. N/10 |
|---|---|---|---|---|---|---|---|---|---|---|
| | C.c. N/10 | % of Total N | C.c. N/10 | % of Total N | | | | | | |
| One-half with 7.6 per cent. lactose (uninoculated) | 23 | 13.5 | 6 | 3.5 | .... | ..... | 10 | ... | 9 | ... |
| Inoculated with Streptococcus lacticus | 27 | 17.8 | 2 | 1.2 | 1.79 | 19.6 | 36 (26) | 110 | 10 (1) | 100 |
| Inoculated with B. coli communior | 21 | 13.1 | 5 | 3.0 | 0.99 | 10.8 | 38 (28) | 246 | 13 (4) | 233 |
| Inoculated with Bac. "A" 90 | 30 | 16.1 | 3 | 1.3 | 0.45 | 4.9 | 60 (50) | 134 | 13 (4) | 121 |
| Inoculated with Bac. "A" 114 | 24 | 14.0 | 2 | 0.9 | 0.81 | 8.9 | 10 (0) | 232 | 6 (0) | 226 |
| Inoculated with Spore-Bearing Bacillus 89 | 146 | 89.0 | 44 | 26.5 | 1.19 | 13.0 | 34 (24) | 202 | 36 (27) | 166 |
| One-half milk with 6.6 per cent. casec (uninoculated) | 39 | 4.9 | 4 | 0.5 | .... | ..... | 14 | ... | 12 | ... |
| Inoculated with Streptococcus lacticus | 134 | 19.3 | 7 | 0.9 | 1.32 | 57.4 | 131 (117) | 206 | 21 (9) | 185 |
| Inoculated with B. coli communior | 516 | 70.0 | 46 | 6.2 | 2.30 | 100.0 | 118 (104) | 242 | 49 (37) | 193 |
| Inoculated with Bac. "A" 90 | 250 | 33.0 | 13 | 1.6 | 2.00 | 87.0 | 195 (181) | 258 | 24 (12) | 234 |
| Inoculated with Bac. "A" 114 | 67 | 8.9 | .. | .... | 0.12 | 5.2 | 25 (11) | ... | .. .... | ... |
| Inoculated with Spore-Bearing Bacillus 89 | 529 | 69.6 | 131 | 17.2 | 1.17 | 50.9 | 55 (41) | 302 | 91 (79) | 211 |
| Fat-free milk (uninoculated) | ... | .... | ... | .... | .... | ..... | 18 | ... | 10 | ... |
| Inoculated with Streptococcus lacticus | ... | .... | ... | .... | .... | ..... | 86 (68) | 126 | 13 (3) | 113 |
| Inoculated with B. coli communior | ... | .... | ... | .... | .... | ..... | 45 (27) | 190 | 10 (0) | 180 |
| Inoculated with Bac. "A" 90 | ... | .... | ... | .... | .... | ..... | 88 (70) | 213 | 13 (3) | 200 |
| Inoculated with Bac. "A" 114 | ... | .... | ... | .... | .... | ..... | 31 (13) | ... | .. .... | ... |
| Inoculated with Spore-Bearing Bacillus 89 | ... | .... | ... | .... | .... | ..... | 42 (24) | 221 | 17 (7) | 204 |

plain milk, is even decreased in the cultures of "Bacillus A" and *Streptococcus lacticus,* but is increased in the milk with the added casec in all the cultures except that of 114. It is also interesting to note that there is never any significant production of volatile acids except in the cultures in which ammonia was produced. Colon bacillus is seen to be alone among these organisms in producing more nonvolatile acids in the milk enriched with lactose than in plain milk or in milk enriched with casein. Whether this difference is sufficiently great to be significant, as well as the differences shown by the other organisms in regard to nonvolatile acid production, is doubtful.

It has not been thought necessary to refer to the results of other studies on bacterial metabolism, particularly the extensive work of Kendall and his co-workers, as the work of others has been carried on from a different point of view from this study.

The following charts (6 to 8 inclusive) show some results of a feeding experiment with white rats, carried out by Dr. Gladys L. Boyd.

## COMMENT

The purpose for which this study was undertaken has been accomplished only in part. A typical intestinal flora in chronic intestinal indigestion, which is unusual for this period of life, is strongly suggestive of a bacterial influence in the etiology. Evidence of abnormal putrefactive activity in the intestines has been obtained in the general finding of a considerably greater ammonia content of the feces in this condition than has been found under any other circumstances except in the feces of infants with serious digestive disturbances as shown in Table 3. Early in the work, a spore-bearing bacillus was isolated from the feces of two children suffering from chronic intestinal indigestion, which at first was proteolytic but which was found to change its nature greatly after long culturing. A considerable number of other spore-bearing bacilli isolated from various stools were examined and found to be only weakly or not at all proteolytic. Several strains of "Bacillus A," the organism predominating in the stools in chronic intestinal indigestion, were isolated, extended studies were undertaken on their metabolic activities, and on those of the before-mentioned spore-bearing bacillus, separately and in conjunction. Control studies were made on *B. coli* and *Streptococcus lacticus.* The medium used was plain or variously modified milk.

Since an increased ammonia production was always found when there was an increased unknown nitrogenous rest fraction of the broken down protein, and as volatile acid production was only found in connection with ammonia production, it has been concluded that ammonia production in a culture is a sign of harmful proteolytic activity.

On this assumption *Streptococcus lacticus* never showed any harmful activity though always metabolically active, as indicated by the amino-acid fraction, the use of sugar, and the titratable acidity in its cultures. Colon only produced ammonia and volatile acids in the casein-enriched milk. The spore-bearing bacillus always showed proteolytic activity in a marked degree except when in its strongly acid producing phase. "Bacillus A" forms were variable in respect to ammonia production but

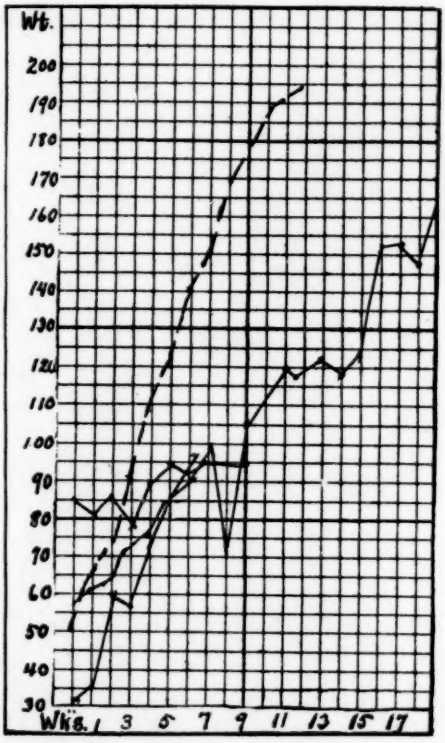


Chart 6.—Rats on milk cultured with Spore 89. The curves are plotted from the weight of white rats fed on whole milk cultured thirty-six hours with Spore 89. The control was fed on autoclaved whole milk. Bread was added to the food of the rats on Spore 89 because they did not take so much milk as did the control. None of the rats showed any symptoms or signs of chronic intestinal indigestion but appeared normal except for their small size. Roentgenograms of the long bones were made but showed only an indefinite line of probable rarefaction. Necropsies revealed no pathologic change other than slight reddening of the shafts of the long bones near the epiphyses. The broken line on this and Charts 7 and 8 represent the weight curves of control rats.

were rarely more than mildly proteolytic when cultured alone. Cultures of different strains of "Bacillus A" and Spore 89 in conjunction, however, sometimes showed marked proteolytic activity. These last observations suggest the possibility of a symbiosis between "Bacillus A" and

Spore 89. However, when the great variability in metabolic activity of "Bacillus A," as well as that of Spore 89, is considered, we are more inclined to see some support for the theory that these forms have a power of transformation. Noguchi was able to bring about such transformation experimentally with typical *B. bifidus* through the doubtful "Bacillus A" forms to a proteolytic spore-bearing bacillus and back again to the original bifidus. It has to be admitted that, so far, in this work no bacteriologic evidence has been obtained to support a relationship between Spore 89 and "Bacillus A" forms. It is also possible that

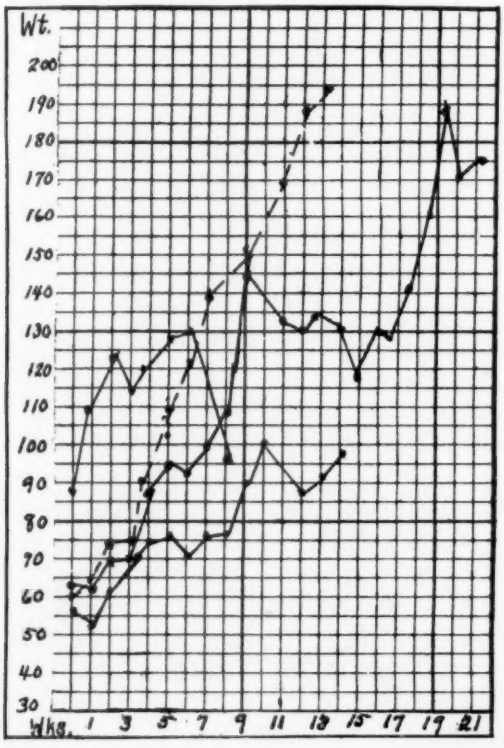


Chart 7.—Rats fed on milk cultured with Spore 89 and then autoclaved three times so that the spore was killed. From this graph it would appear that the killed spore was even more effective in inhibiting or delaying growth than the living ones. The only change in the appearance of the rats was a temportary loss of hair. The necropsy showed slightly enlarged but otherwise normal livers. They were negative otherwise.

other spore-bearing bacilli from the stools might have shown a similar variable character as this one if they had been studied in the same way. It is hoped later to repeat Noguchi's work with our "Bacillus A" and also to see if Spore 89 under the conditions established by Noguchi can be made to undergo the transformation he found in the case of *B. bifidus*.

Noguchi's work has been confirmed by that of Howe and Hatch [14] with organisms isolated from the mouths of nurslings. In this connection it is interesting that Kendall [15] described *B. infantilis* as a very active producer of ammonia and a primary amin which are neutralized by volatile acids simultaneously produced, and that in isolating it he found radically different types of bacteria producing colonies that were indistinguishable, and that certain colonies were formed of two kinds of bacteria.

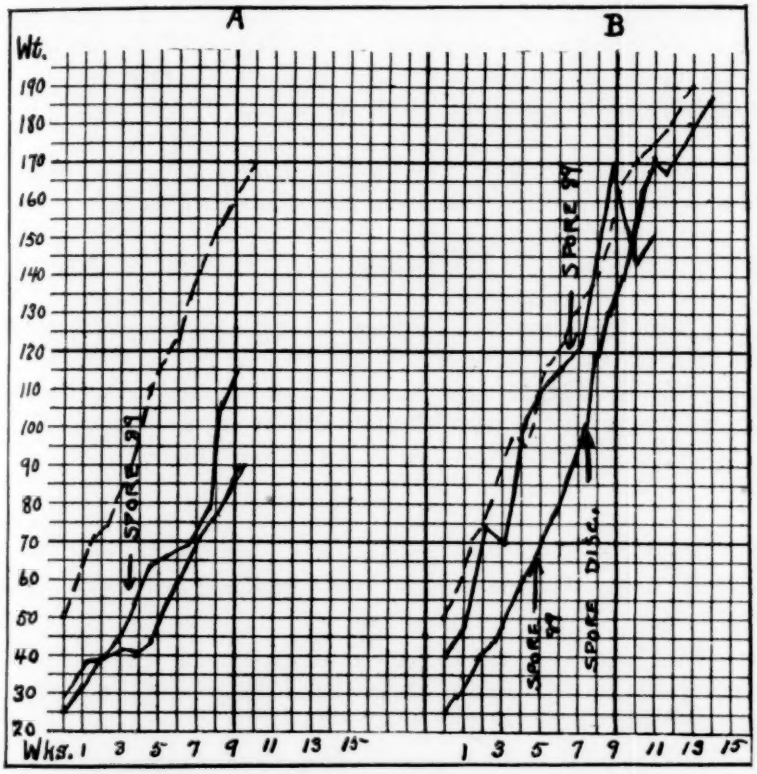


Chart 8.—Rats fed on *A*, milk cultured with *Streptococcus lacticus*, and *B*, acidified milk. These charts show the inhibiting effect of *Streptococcus lacticus* milk and milk to which lactic acid has been added on Spore 89. The rats grew as rapidly as did the control, and the introduction of Spore 89 into the food at a later date was without effect.

In another article, his discussion of the adaptation in the intestines of spore-bearing bacilli to long continued, carbohydrate feeding seems also to have a bearing on the subject.[16]

14. Howe, P. R., and Hatch, R. E.: J. M. Res. **36**:481, 1917.
15. Kendall, A. I.: J. Biol. Chem. **5**:419-439, 1908-1909.
16. Kendall, A. I.: J. Biol. Chem. **6**:499, 1909.

Our rat-feeding experiment is also only suggestive as regards this spore-bearing bacillus as a factor in the etiology of chronic intestinal indigestion, for some other spore-bearing organisms under the same circumstances might produce the same effect.

The work reported in Table 13 was undertaken in the hope of finding some advantages in the casein-enriched milk to *Streptococcus lacticus* and disadvantages to the supposedly harmful bacteria under consideration. The results are not particularly enlightening. It is true that *Streptococcus lacticus* was highly active in the high protein medium and produced no ammonia nor volatile acids worth mention, but the other forms studied, except 114, were also active and they produced ammonia in quantity in this medium. The plating out of the residue of the cultures in this medium showed all the organisms except the spore form in vigorous growth. The latter gave a much smaller number of colonies than any of the others and only about half the number that it gave in the lactose-enriched milk. "Bacillus A" 114 seemed to be rather inactive metabolically in both mediums, but plating the residues showed abundant growth in the high protein and comparatively slight growth in the high sugar medium. Torrey [17] states that streptococci in the intestines are stimulated by casein and that feeding experiments with casein indicated that the large numbers of streptococci in the feces with a milk diet were due more to its casein than to its lactose content. This is interesting in view of our clinical and chemical findings.

## SUMMARY

1. That a predominantly gram-positive aciduric intestinal flora of *B. bifidus* type is characteristic of chronic intestinal indigestion has been confirmed.

2. That proteolytic activities are concerned in the production of the symptoms of chronic intestinal indigestion is indicated by the abnormally high ammonia content of the feces.

3. A highly proteolytic spore-bearing bacillus, isolated from the stools in two cases of chronic intestinal indigestion, has been found to be capable of extreme changes in the nature of its metabolic activities (in milk).

4. "Bacillus A" forms, which constitute the predominant organisms of the typical flora in chronic intestinal indigestion are also variable in their metabolic behavior (in milk), though when cultured alone they are not usually strongly proteolytic.

5. Some support is given by this work to the theory that a transformation of one to the other of *B. bifidus*, "Bacillus A" forms and a

17. Torrey, J. C.: J. M. Res. **39**:415, 1918-1919.

spore-bearing bacillus, such as Noguchi brought about experimentally, may take place in the intestinal tract under some circumstances.

6. Some feeding experiments with white rats showed that they did not gain normally while being fed milk cultures of the before-mentioned spore-bearing bacillus but resumed the normal rate of gain as soon as the diet was changed. Cultures of the other organisms did not interfere with normal growth. Acidified milk and culturing with *Streptococcus lacticus* inhibited the growth depressing effect of Spore 89.

7. *Streptococcus lacticus* (*Micrococcus ovalis*), the organism used in the preparation of the lactic acid and protein milk, which forms a part of the special high protein diets used in the treatment of chronic intestinal indigestion, establishes itself as the predominant organism of the feces soon after its ingestion has been begun. It probably, however, takes a long time for it to oust completely the offending flora, which perhaps persists in a spore form.

8. *Streptococcus lacticus* was very active metabolically in casein-enriched low sugar milk and formed no harmful products.

# TETANY AS A CAUSE OF CONVULSIONS IN WHOOPING COUGH *

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The so-called nervous complications of whooping cough are well recognized; they generally have been attributed to asphyxia, cerebral edema or congestion, brain injury from hemorrhage, encephalitis or meningitis. The symptomatology of these various forms of injury is, of course, manifold, but the outstanding symptom and the one usually present and common to all is convulsions. As a matter of fact, however, the rarity with which definite pathologic lesions are proved to exist is in rather striking contrast to the frequency with which convulsions occur. Indeed, it would seem quite probable that the existence of convulsions in whooping cough has frequently been the principal basis on which a diagnosis of cerebral hemorrhage, encephalitis or other lesion, has been set up. It is the purpose of this paper to call attention to the fact that infantile tetany, and not anatomic injuries or an unknown toxin, is often the cause of the convulsions in whooping cough. The wide recognition of this fact is important because the convulsions of pertussis, in which death not infrequently occurs, may be amenable to adequate treatment when the patient has tetany.

## CASE REPORTS

CASE 1.—M. D., a girl aged 4 months, Italian, was admitted to New Haven Hospital, March 2, 1922. The family history was unimportant.

Past History: Birth was normal, except for the use of instruments. Breast feedings were attempted but as the baby refused to nurse well, feedings of cow's milk were then given. The child was "always nervous and irritable and cries a good deal; does not cry after feedings. Since birth, when she would cry, she would often lose her breath, turn blue and have to be whipped to cause her to catch her breath."

Present Illness: About the middle of February, the patient developed an infection of the upper respiratory tract, with a cough which became severe and finally paroxysmal. The baby lived in the same house with her cousins (family of R. M., Case 2 of this series), two of whom had pertussis. The baby had several severe convulsions on the day preceding admission to hospital.

Course in Hospital: On examination, the baby did not look very sick; she was well nourished. There was a paroxysmal cough of moderate severity; marked craniotabes; slight enlargement of epiphyses of wrists and of costochondral junctions. Chvostek's sign was present but was not well marked. The temperature was elevated and there were signs of bronchopneumonia. The fever continued and ranged irregularly from 38 to 40 C. (from 100 to 104 F.) throughout the illness. The child became very toxic, the pneumonia extended and death occurred March 14.

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* From the Department of Pediatrics, Yale University School of Medicine.

*Comment.*—On the day after admission, the patient had several convulsions; no further attacks occurred after the administration of calcium chlorid was well established. Examination of the blood taken on the day of admission (patient febrile) showed total calcium concentration in the serum of 4.9 mg. per hundred cubic centimeters. Roentgenograms of the extremities showed none of the usual signs of rickets.[1]

The diagnosis was whooping cough, infantile tetany, rickets and bronchopneumonia.

CASE 2.—R. M., a boy, aged 11 months, Italian, was admitted to New Haven Hospital Feb. 27, 1922. The family history was unimportant except that an older sister had whooping cough.

Past History: The child was born at term; delivery was normal. He was breast fed from birth, and also received bread and soup occasionally.

Present Illness: Two weeks preceding admission to hospital, the patient showed symptoms of upper respiratory tract infection; these were followed by paroxysmal cough. He seemed to be doing well until the day of admission, when he had a series of four generalized convulsions.

Course in Hospital: On admission, examination showed a fat baby with moderately severe whooping cough. There was bilateral otitis media, also slight enlargement of the parietal bosses and of the epiphyses of the wrist. No carpopedal spasm, Chvostek's sign or Trousseau's sign was present. The child had an irregular temperature, ranging between 37 and 39 C. (98 and 102 F.) during first week in hospital; the fever then became gradually lower and reached normal before the patient was discharged. Many slight convulsions occurred during the first four days in hospital; these were followed by several severe convulsions. Chvostek's sign became positive on March 4, and was present when the patient was discharged. Calcium chlorid was given throughout the period the baby was in hospital but the doses at first were inadequate. The patient was discharged March 12, in good condition, but the paroxysmal cough was still present.

The child was readmitted, March 20, because of fever and "blue spells." The fever was due to measles. He was never very ill and the disease ran an uneventful course. On April 7 (patient afebrile), the total calcium concentration in the blood serum was 7.6 mg. per hundred cubic centimeters. The child was discharged April 9, in good condition.

Diagnosis: First admission, whooping cough, infantile tetany, rickets and otitis media. Second admission: measles and infantile tetany.

*Comment.*—It is unfortunate that there is no record of a calcium determination on the blood of this patient during his first hospital period. A diagnosis of tetany was made, presumably, since the clinical data are hardly adequate, on the basis of unrecorded laboratory data known to the physician in charge. During a second hospital period, a few weeks after the first, a calcium determination on blood serum obtained when the baby was afebrile, and while calcium chlorid was being administered, showed 7.6 mg. per hundred cubic centimeters. It seems altogether likely, therefore, that the convulsions during whooping cough as well as those during measles were due to tetany.

CASE 3.—P. C., a boy, aged 16 months, one of twins, Italian, was admitted to New Haven Hospital March 8, 1922.

The family history was unimportant except that the twin brother, who had whooping cough, high fever and otitis media, died in convulsion on the day preceding the patient's admission to hospital. After the severe attacks of cough-

1. It is greatly regretted that electrical reactions and spinal fluid examinations could not be obtained on all of the patients in this series.

ing, the child was said to have often been unconscious for considerable periods of time.[2]

Past History: Birth was normal. The child was breast fed for five months; cow's milk and various solid foods were given after the patient was weaned; green vegetables and orange juice were never given. The child was subject to frequent respiratory infections.

Present Illness: On February 11, the baby was taken ill with infection of the upper respiratory tract accompanied by a cough which became increasingly severe and of paroxysmal nature. At times the attacks resembled convulsions; he had three convulsions just prior to the onset of whooping cough.

On admission to the hospital, it was seen that the child was very ill and had a severe paroxysmal cough. The temperature was elevated but this was satisfactorily accounted for by the presence of severe otitis media. There were slight evidences of rickets. No laryngeal spasm, carpopedal spasm, Trousseau or Chvostek's signs were present. The calcium in the blood serum, March 8 (patient febrile), was 8.9 mg. per hundred cubic centimeters.

Course in Hospital: The patient's temperature was irregular for several days, never higher than 39 C. (102.2 F.) then became normal. Calcium chlorid and cod liver oil were given throughout the period in hospital, during which time no convulsions were observed. The cough improved but was still present when the baby was discharged, in fair condition, on March 18.

The patient was readmitted March 25, seriously ill with measles; the temperature was continuously high, and extensive bronchopneumonia was present. The child died April 3.

During the period of the second hospital admission, the baby had two convulsions, although calcium chlorid was given daily. On March 27, the total calcium in the blood serum was 7.9 mg. per hundred cubic centimeters.

Diagnosis: First admission — whooping cough, latent tetany, rickets and otitis media. Second admission, active tetany, measles and bronchopneumonia.

*Comment.*—This patient had convulsions at about the time of onset of whooping cough, early in the disease and again during the course of measles; convulsions played no part in the symptomatology of whooping cough while the patient was in the hospital. Although the calcium content of the serum when the patient was first admitted was 8.9 mg., a determination during the second admission, when the convulsions were present and calcium chlorid was being given, was 7.9 mg. It seems thus probable that the patient had tetany, at times latent and at times manifest.

CASE 4.—C. T., a girl, aged 17 months, Italian, one of twins (other twin, E. T., Case 5 of this series), was admitted to New Haven Hospital, March 2, 1925.

The family history was unimportant. The past history showed that the delivery was normal. The child was breast fed for eight months; since weaning, the diet had been cow's milk, bread, butter, macaroni and orange juice. No cod liver oil was given.

Present Illness: On February 15, two weeks before admission to hospital, the patient had a series of convulsions extending over a period of two days. The physician made a diagnosis of whooping cough and pneumonia. No further convulsions occurred until the day before admission, when the patient began another series of attacks which continued off and on until controlled in the hospital by drugs.

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2. In view of the findings reported in the cases in this series, it seems highly probable that this child had infantile tetany. Dr. D. W. Porter has told me of a baby, aged 18 months, who was admitted to the hospital because of severe whooping cough complicated by pneumonia; the patient died shortly after admission. This patient had been treated previously by Dr. Porter for convulsions due to tetany; during the pertussis the convulsions recurred.

On admission, examination showed an extremely sick child with high fever, convulsions, bronchopneumonia, bulging ear drums and marked rickets. The reflexes were active; there was no ankle clonus. No laryngeal spasm, no carpopedal spasm, no Chvostek and Trousseau's signs were present. The eye grounds were normal.

Electrical reactions in milliamperes: cathodal closure contraction, 3; anodal closure contraction, 4; anodal opening contraction, 2.5; cathodal opening contraction greater than 5.

Blood taken on the day of admission (patient febrile) showed total calcium concentration of 8.9 mg. per hundred cubic centimeters of serum; inorganic phosphorus concentration of 2.5 mg.

Spinal puncture on admission yielded 20 c.c. of clear fluid, containing 7 cells per cubic millimeter, and giving a slightly positive globulin reaction (Pandy).

The patient was given calcium chlorid and sedative drugs, and the convulsions were kept under control. The baby was extremely ill, with a continuously high temperature, and died March 4.

*Necropsy.*—At necropsy, extensive bronchopneumonia, with no evidence of cerebral injury was found.

In regard to the brain, Dr. Buckley's note is as follows: "The brain weighs 450 gm. Externally and on section there is no abnormality noted except in the lenticular nuclei, in which spaces about the small blood vessels are prominent."

Diagnosis: Whooping cough, infantile tetany, rickets, bronchopneumonia and otitis media.

CASE 5.—E. T., a girl, aged 17 months, Italian, one of twins (other twin C. T., Case 4 of this series), was admitted to New Haven Hospital, March 3, 1925.

The family and the past history were essentially the same as those of C. T., Case 4.

Present Illness: The patient became ill about the same time as her twin sister, two weeks before admission to hospital, with a cold, fever and a paroxysmal cough; the physician made the diagnosis of pneumonia and whooping cough. The child had no convulsions at this time and in few days was better except for the severe cough. On the day of admission, however, the baby had a series of generalized convulsions and for this reason was brought to hospital.

On admission, examination showed a very sick child in a convulsive state, with a temperature of 38.5 C. (101 F.). Carpopedal spasm was present throughout the examination and was exaggerated during convulsive seizures. At times, there was an inspiratory crow; there were also signs of marked rickets, and bronchitis and bilateral otitis media. Chvostek's sign was not present. Electrical reactions showed anodal irritability and reversibility; cathodal opening contraction was not obtained with the current less than 5 milliamperes. The calcium concentration of the blood serum (patient febrile) was 7.7 mg. per hundred cubic centimeters, and inorganic phosphorus was 2.9 mg. Lumbar puncture was done but blood tinged fluid was obtained.

Course in Hospital: The ears were opened and the temperature became gradually lower, remaining at about 37.5 C. for one week, it then began to rise and reached 41 C. (105.8 F.). Signs of bronchopneumonia were present. The baby was critically ill for several days but had no convulsions. Calcium chlorid and cod liver oil were administered daily; ultraviolet irradiation also was used. The baby slowly improved and was discharged March 28 in good condition, although the proxysmal cough persisted.

Diagnosis: Whooping cough, infantile tetany, rickets, bronchopneumonia and otitis media.

SUMMARY OF DATA

No data of a clinical nature are presented in this paper which are not found in the articles on whooping cough in the standard textbooks.

In whooping cough, convulsions occur most frequently in very young patients—"in teething infants,"[3] and in "those of tender age."[4] In this series of patients, the youngest was 4 months and the eldest 17 months of age.

The subjects of convulsions in pertussis are usually rachitic infants.[5] Of the patients here reported, three had severe rickets and the other two had definite signs of the malady.

Convulsions may occur at any time in the course of whooping cough; they may be coincident with the onset of the disease itself or of a complication, or without relation to either; they may occur in severe cases or in cases otherwise benign. The convulsions rarely occur singly; there is usually a series of attacks. Most of these points are illustrated in the case reports.

There are usually concomitant "inflammatory complications."[4] Apparently, convulsions are likely to occur in those infants who have pneumonia[5] with pertussis. The convulsions occur most frequently during fever. In the present series of cases, all of the patients had fever, all but one had otitis media and three of the five had bronchopneumonia.

Whooping cough complicated by convulsions in infants becomes an exceedingly serious malady and often ends fatally; the prognosis is always grave. The mortality is 72 per cent., according to statistics from the Pediatric Clinic in Munich (see footnote 8). In the five cases reported here, two patients died, both of whom had bronchopneumonia.[6] One patient with bronchopneumonia survived. None died of convulsions *per se*, although death under these circumstances is said to be frequent.

The electrical reactions of two infants, the only ones on whom determinations were made, were strongly suggestive of tetany in that they showed anodal hyperirritability.

In one case, the spinal fluid was examined and was found to be negative. Meningitis and cerebral hemorrhage were thus eliminated as possible causes of convulsions in that patient.

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3. Kerr, C. B.: Infectious Diseases, London, Oxford University Press, 1920.

4. Trousseau, A.: Lectures in Clinical Medicine, Vol. 1, London, New Sydenham Society, 1868.

5. Holt, L. E., and Howland, J.: Diseases of Infancy and Childhood, New York, D. Appleton & Company, 1923. Griffith, J. P. C. The Diseases of Infants and Children, Philadelphia, W. B. Saunders Company, 1919.

6. A third patient (P. C.) died during a second admission, but the cause of death was bronchopneumonia secondary to measles.

The laboratory findings show that in all of the patients the calcium concentration in the blood serum was less than the accepted normal of 10 mg. per hundred cubic centimeters.[7] The lowest value obtained was 4.9 mg. per hundred cubic centimeters of serum (M. D., Case 1) and the highest, 8.9 mg. This latter value was obtained for the serums of P. C. (Case 3) and of C. T. (Case 4). Both M. D. and C. T. were very ill with complicating infections to which they ultimately succumbed. M. D., however, who was having only infrequent convulsions, had a serum calcium of one-half that of C. T., who was in a more or less continuous convulsive state. P. C. (Case 3) was moderately ill at the time the first calcium determination (8.9 mg.) was made. Later, when this baby returned with measles and pneumonia, although she had been receiving some calcium chlorid, her serum calcium was low (7.9 mg.) and she was having convulsions at times. E. T. (Case 5) was having frequent convulsions, and yet the calcium in her blood serum was not very low, 7.7 mg. per hundred cubic centimeters.

## COMMENT

The cause of the convulsions in the cases reported in this series might be attributed by different observers to various disturbances, some with and some without alleged anatomic basis. Many clinicians would ascribe the attacks to a "toxin" [8] or to "a peculiar susceptibility of the patient brought about by the disease itself." (Holt and Howland, footnote 5.) This attitude was admirably stated in 1868 by Trousseau [4] in his lecture on "whooping-cough."

> Convulsions may come on also independently of hemorrhages and of congestion. They are then due to the nervous element which gives to whooping cough its specific character; the nervous excitability which already manifests itself, as a rule, by the production of convulsive fits of coughing, spreads to the whole system, either in consequence of the weakness of the patient's constitution, or of acquired weakness, his strength having been exhausted by the prolonged duration of the complaint, by disordered nutrition, or any other cause. These nervous accidents, which sometimes also consist of *delirium* and of *extreme agitation*, are more frequent and more grave in proportion to the tender age of the child. They nearly always terminate fatally when they coincide with the inflammatory complications.

However, in the cases described, taking into account the clinical phenomena exhibited, the response to therapy and the laboratory data, the diagnosis of infantile tetany is established beyond much question. Thus, "the nervous element which gives to whooping cough its specific

7. Unless otherwise stated, reference is made only to the admission determinations before calcium chlorid treatment.

8. Husler, J., and Spats, H.: Die Keuchhusten-Eklampsie, Ztschr. f. Kinderh. **38**:428, 1924.

character" [4] is the same, for a considerable number of infants with pertussis and convulsions, as that which underlies the symptom-complex known as tetany.

According to the criteria set up by Howland and Marriott,[9] and pretty generally accepted as standard, the diagnosis of manifest tetany is not established in these patients by the laboratory data, excepting for M. D. These investigators state that "when there are convulsions and other symptoms due to tetany, the calcium of the serum is 7.0 mg. or less per hundred cubic centimeters." [9] Some of the cases here reported would be regarded as latent, rather than as manifest, tetany if judged by this standard. However, it seems to me that the diagnosis of tetany was correctly made in all of the patients, and that the criteria established by Howland and Marriott ought not to be too stringently applied. Indeed, not all investigators agree that there is a strict parallelism between the severity of the symptoms of tetany and the degree of diminution of the calcium concentration in the serum. The ionized rather than the total calcium may perhaps be the important determining factor in this connection.[10] Anderson and Graham [11] state that "active tetany is always accompanied by a diminished calcium content of the serum. The severity of the tetany, however, bears no relationship to the diminution of the calcium." Woringer [12] found that the average of a series of calcium determinations in severe cases of tetany was 6.6 mg: per hundred cubic centimeters of serum; in cases of medium severity, 6.6 mg., and in cases of slight severity 6.4 mg. Woringer's conclusion on this point is of interest. "Hypocalcemia is more marked in manifest tetany, in laryngospasm and infantile eclampsia than in latent tetany. The diminution in the calcium bears no direct relationship to the severity of the disease. It appears that other factors, fever, emotional states, etc., along with diminished blood calcium, have something to do with precipitating convulsions." [13]

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9. Howland, J., and Marriott, W. McK.: Observations Upon the Calcium Content of the Blood in Infantile Tetany and Upon the Effect of Treatment by Calcium, Quart. J. Med. **11**:289 (July) 1918.

10. Gamble, J. L., and Ross, G. S.: Studies of Tetany. II. The Effect of Ingestion of Hydrochloric Acid Producing Substances on the Acid-Base Metabolism of an Infant and the Probable Manner of Their Action in the Treatment of Tetany, Am. J. Dis. Child. **25**:470 (June) 1923.

11. Anderson, G. H., and Graham, S.: Some Factors Concerned in the Etiology of Tetany in Children, Quart. J. Med. **18**:62 (Oct.) 1924.

12. Woringer, P.: Hypocalcémie et Spasmophilie, Arch. de méd. d. enf. **26**:713 (Dec.) 1923.

13. L'hypocalcémie est plus prononcée dans les formes manifestes de la maladie, tétanie, laryngospasme et éclampsie, que dans la forme latente. Elle n'est pas en rapport direct avec la gravité de la maladie. Il semble, qu'à côté de l'abbaissement du calcium sanguin, d'autres causes entrent encore en action pour déclencher le syndrome convulsif, telles que la fièvre, les émotions, etc.

The possible etiologic relationship of tetany to the convulsions of pertussis is not a new subject so far as the German literature, at least, is concerned. German authors, however, are by no means in agreement as to the importance of tetany in this connection. Neurath [14] wrote in Pfaundler and Schlossmann's "Handbuch," second edition (1910), as follows: "The convulsions are regarded by many authors as the expression of a latent tetany (spasmophilia) which has become manifest through the influence of a severe illness." [15] But Knöpfelmacher,[16] writing in the third edition (1923), of the same "Handbuch," seemed to minimize the etiologic rôle of tetany.

> It is accepted that the course of whooping cough in the infant may be influenced by a latent spasmophilic diathesis. Wernstedt investigated a series of infants with whooping cough with regard to the electrical reactions; he found that contractions were obtained with small values of the galvanic stimuli (anodal opening contraction 2.4 ma.) in children with severe attacks of the disease. The accuracy of this finding was denied by Erlanger. Pospischill was unable to observe any relationship between tetany and pertussis.[17]

In 1920, Reiche [18] reported twenty-nine cases of pertussis with convulsions; most of the patients died and were examined postmortem. As the result of the clinical findings and the necropsies in these patients, Reiche stated his attitude in regard to the relationship between tetany and convulsions in whooping cough as follows:

> We are unable to accept the conception sponsored by Feer, Finkelnburg, Reyer, Krause and Neurath, that an abnormally increased irritability of the nervous system, designated as spasmophilia, is the basis for the convulsions.[19]

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14. Neurath, R.: Whooping Cough in Pfaundler and Schlossmann's Handbuch der Kinderheilkunde, Ed. 2, Leipzig, F. C. W. Vogel, **2**, 1910.

15. Die Konvulsionen sind nach der Ansicht mancher Autoren als der Ausdruck einer latenten Tetanie (Spasmophilie), die unter dem Einfluss der schweren Erkrankung zu manifesten Symptomen führt, aufzufassen. Similar statements are made by Feer (Lehrbuch der Kinderheilkunde, Zweite Auflage, Jena, G. Fischer, 1912) and Finkelstein (Lehrbuch der Säuglingskrankheiten, Zweite Auflage, Berlin, J. Springer, 1921).

16. Knöpfelmacher, W.: Whooping Cough in Pfaundler and Schlossmann's Handbuch der Kinderheilkunde, Ed. 3, Leipzig, F. C. W. Vogel, 1923.

17. Es wird angenommen, dass die Verlaufsform des Keuchhustens beim Säugling durch eine latente spasmophile Diathese beeinflusst werden kann (Finkelstein). Wernstedt hat eine Reihe keuchhustenkranker Säuglinge auf ihre elektriche Erregbarkeit untersucht und gefunden, dass ausgeprägte Anfälle bei Kindern mit niedrigen Zahlen der galvanischen Erregbarkeit einhergehen (A Ö Z < 2, 4 MA), was aber von Erlanger bestritten wird. Pospischill hat eine gegenseitige Beeinflussung bestehender Tetanie und Pertussis nicht beobachten können.

18. Reiche, F.: Keuchhustenkrämpfe, Ztschr. f. Kinderh. **25**:28 (May) 1920.

19. Auch der von Feer, Finkelnburg und Reyher vertretenen, von Krause und Neurath miterwähnten Auffassung, dass eine abnorme Veranlagung, die als Spasmophilie bezeichnete krankhaft gesteigerte Reizbarkeit des Nervensystemes den Konvulsionen zugrunde liege, vermögen wir nach unseren Erfahrungen nicht beizupflichten.

In 1924, Husler [8] stated that about 10 per cent. of patients with whooping cough and convulsions had tetany.

Confusion seems to exist in the older literature, because a clear distinction between laryngeal spasm as a symptom of tetany and as the whoop of pertussis is not made.

It would seem that the question under discussion could be very definitely settled if electrical reactions and blood calcium determinations were made the criteria on which a diagnosis of tetany is established. Clinical manifestations of tetany in patients with whooping cough and tetany are often absent but tetany cannot therefore be said to be absent. Pertussis, the most prolonged of all the infectious diseases, "is the one in which convulsions are most frequent." ( Holt and Howland, footnote 5.) These convulsions may have, no doubt, a variety of causes and in infancy the principal etiologic factors may not be those common in early or in late childhood. It has been amply demonstrated that definite cerebral lesions of various kinds occur in whooping cough. The point to be stressed is, that as more is known about tetany, and particularly about the relation of febrile disturbances [20] to it, tetany will probably be shown to exist with increasing frequency. It is perhaps of significance in this connection to note that the principal age incidence of pertussis complicated by convulsions is the same as that of infantile tetany and of rickets with which tetany is intimately associated.

The calcium concentration of the blood and the electrical reactions of all infants with whooping cough should be determined if possible, and therapeusis guided by the evidence for or against the existence of latent tetany. In the event that these determinations cannot be made, calcium chlorid should be administered to young children who have whooping cough complicated by convulsions, even if there is no clinical evidence of tetany and rickets; exception to this procedure might be made, of course, in those patients with proved cerebral lesions. Furthermore, it would seem highly advisable, regardless of clinical signs or of laboratory data, to treat all infants suffering from whooping cough with cod liver oil or radiant energy or both. Even when uncomplicated, the infection is often severe and the therapeutic measures just mentioned will not only prevent and cure rickets on which infantile tetany is usually, if not always, engrafted, but also promote general physical welfare more

20. Kraemer, Tisdall and Howland (Am. J. Dis. Child. **22**:560 [Dec.] 1921) found normal values for the calcium concentration of the blood of patients with various febrile diseases but without tetany. Gerstenberger, Burhans, Smith and Wetzel (Am. J. Dis. Child. **26**:329 [Oct.] 1923) found a slightly diminished blood calcium in some nonrachitic patients with pneumonia without tetany. The literature contains reports of results which are not in accord with those of Kraemer, Tisdall and Howland who discuss critically the conflicting data.

effectively than any so-called "tonic remedies." As is well recognized, infections of any kind are particularly severe in patients with rickets and its frequent associates, tetany and anemia. The prognosis for those infants with whooping cough complicated by convulsions should be improved by appropriate treatment if the attacks are due to tetany, although the outlook may still be grave.

## CONCLUSIONS

1. The convulsions which frequently complicate pertussis in babies are often manifestations of infantile tetany.

2. Electrical hyperirritability of the nerves and a reduced calcium concentration of the blood serum may be the only means of recognizing the existence of tetany.

3. A recognition of the rôle of tetany in this connection is important, in order that appropriate therapy for preventative as well as for curative purposes may be instituted.

# A FREQUENT CAUSE OF DYSPEPSIA IN BREAST FED INFANTS*

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Quite frequently, one observes breast fed infants who, after doing well for the first few weeks or months of life, stop gaining in weight, and become restless and irritable. The stools are either small and dark colored, or frequent, loose and foul smelling. Mucus and fat curds may be present. Vomiting, occasionally severe, may be a predominating symptom. Ultimately these infants lose weight, and unless proper treatment is instituted they become distinctly athreptic. The symptoms enumerated are commonly designated by the term "dyspepsia."

## CAUSE

Overfeeding at the breast has been considered a frequent cause of the symptoms observed, especially in those infants in whom diarrhea has been a prominent symptom. It is undoubtedly true that breast fed infants occasionally receive more milk than is necessary to cover their requirements, but in such cases the infant usually spits up a certain amount and continues to thrive. In my experience, overfeeding with breast milk is a rare cause of dyspepsia.

Faulty composition of mothers' milk does not seem to be a factor in the causation of the symptoms of dyspepsia. In the series of cases at our hospital, the breast milk was analyzed and the figures for sugar, fat and protein were not found to differ from those of the milk of mothers whose babies were thriving.

Lederer [1] states that the milk of mothers who were themselves underfed, due to war conditions, was occasionally low in both fat and sugar content, and that the infants of these mothers presented the symptoms of dyspepsia.

Various parenteral infections, of course, lead to dyspeptic symptoms, usually of an acute nature; but in the group of infants which I have observed, no evidences of infection were present.

The symptoms of dyspepsia cannot be attributed to constitutional anomalies because of the fact that the infants respond rapidly to proper treatment.

In a group of thirty-three infants, in whom the symptoms enumerated were present, it was found in each instance that the mother was secreting

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1. Lederer, R.:, Ztschr. f. Kinderh. **31**:141 (Dec.) 1921.

an insufficient amount of milk. Even when the breasts were completely emptied following each nursing, the total amount of milk available was distinctly below that needed to cover the caloric requirements of normal infants. When suitable supplementary feedings were given to these infants, a prompt disappearance of the symptoms occurred regularly. The supplementary feedings given were either two-thirds milk with 5 per cent. added sugar or the "normal milk formula" of Frølich.[2]

Partial inanition may lead to a variety of symptoms, including weight loss, weakness and constipation, as well as dyspeptic symptoms. We observed dyspeptic symptoms in 57 per cent. of a group of infants subjected to partial inanition.

Variot [3] drew attention to the fact that vomiting is a frequent symptom of underfeeding. In recent years it has been recognized in American clinics that many of the customary milk formulas fed to infants provide an insufficient number of calories and, further, that the caloric needs of undernourished infants per unit of body weight are markedly higher than in the case of normal infants (Marriott [4]).

It has further been shown that inanition is an essential factor in producing the condition of athrepsia.[5] The factor of qualitative starvation (lack of vitamins) in bringing about the development of the nutritional disturbances has been emphasized by Frølich.[2]

Inanition is far more serious in the case of an infant than in an older person. The infant has a higher energy requirement as well as a greater need for material for building up new tissues. Furthermore, the infant does not store a sufficient amount of reserve food to supply its needs for any considerable time.

## ETIOLOGY

It is known that rapid destruction of body tissues occurs in infants having an insufficient caloric intake. Young animals subjected to complete starvation die in a much shorter time than older animals, and before as great a loss of body weight has occured (Chossat,[6] Aron,[7] Magendie [8]). Starving young animals often show symptoms similar to those of the infants described. It is our belief that the dyspeptic symptoms occurring in the infants of the type described can be explained on the basis of "hunger."

2. Frølich: Acta Pediat. **4**:76, 1924.
3. Variot: La Clinique Infantile, 1910, No. 22.
4. Marriott, W. McK.: Some phases of the Pathology of Nutrition in Infancy, Am. J. Dis. Child. **20**:461 (Dec.) 1920.
5. Utheim, K.: J. Metabol. Res. **1**:803 (June) 1922.
6. Chossat, Charles: Recherches expérimentales sur l'inanition, Paris, Imp. royale, 1843.
7. Aron: Biochem. Ztschr., 1910.
8. Magendie: Acc. to Rosenstern: Erg. der Inn. Med. und Khk. Bd. 7.

The infants are restless, sleepless, irritable and always crying. There seems to be abdominal pain and discomfort usually regarded as "colic," or "cramps." According to the work of Carlson,[9] these are symptoms of hunger. He has shown that hunger contractions occur in new-born infants even before being fed, and that when such contractions become vigorous the sleeping infant wakes, becomes restless and cries. The hunger periods are more frequent in infants than in adults. He furthermore demonstrated a marked general increase in the excitability of the spinal cord occurring simultaneously with the strong hunger contractions of the stomach. Carlson [10] has further shown, on experimental animals, that gastric hunger contractions appear when the blood sugar falls below 0.07 and 0.08 mg. per hundred cubic centimeters of blood. We made blood sugar determinations on a number of the infants in our series, following short fasts, and have found the blood sugar level to fall to 0.05 and 0.06 mg. and in one case to as low as 0.03 mg. per hundred cubic centimeters. Hypoglycemia occurring in those starved infants is doubtless a factor in bringing about the hunger contractions and general increased irritability.

In experimental animals as well as in infants, diarrhea is a frequent result of starvation. It has been shown by Busch,[11] Boldyreff [12] and Carlson,[9] that the whole intestinal tract undergoes rhythmic contractions during the period of gastric hunger contractions. Such contractions lead to diarrhea. Furthermore, there is a decreased secretion of digestive juices (especially of gastric acid) during starvation (Rosemann [13]). The antiseptic effect of the gastric juice is thus diminished and conditions become favorable for bacterial activity.

Nausea and vomiting are frequent symptoms of hunger, even in adults. Infants, in general, vomit more readily than older people, and with the marked hunger phenomena that they exhibit it is not surprising that vomiting should occur.

The following cases are characteristic and are selected from the series of thirty-three infants observed.

### REPORT OF CASES

CASE 1.—The birth weight was 3,500 gm. The child had always been breast fed, and throve for the first two weeks of life, then became constipated. The stools were dark and foul smelling; one week later they became diarrheal. At the age of 5 weeks, the infant began to vomit after meals. The vomiting was at times projectile. From the sixth to the eighth week of life very little food was retained. There was no fever at any time.

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9. Carlson, A. J.: The Control of Hunger in Health and Disease, Chicago, University of Chicago Press, 1916.
10. Carlson, A. J.: Am. J. Physiol. **69**:117, 1924.
11. Busch: Noted by Carlson, Footnote 9.
12. Boldyreff, Noted by Carlson, Footnote 9.
13. Rosemann: Virchows Arch. f. path. Anat. **67**:229, 1920.

The infant was admitted to hospital at the age of 8 weeks. The weight at that time was 3,360 gm. Aside from the undernutrition, the physical examination was negative.

The mother continued to nurse the baby six times daily. Complementary feedings of a two-thirds whole milk formula were given. The infant had, on an average, 400 c.c. of breast milk, and 240 c.c. of the complementary feeding. Following this regimen, the vomiting stopped, the stools became normal and the infant was discharged thirteen days after admission, having gained 150 gm. in weight.

CASE 2.—A girl, born at term, weighed 3,000 gm. at birth. She was nursed every three hours during the first week of life. The stools became diarrheal in character, were green and were often mixed with mucus. There was no vomiting. The infant was very restless and cried a great deal. At the age of 7 weeks the weight was 3,520 gm. The skin was pale, gray, and inelastic. The physical examination otherwise was negative.

The infant obtained on an average only 30 gm. of breast milk at nursing. Following the nursing, no milk could be expressed from the mother's breasts. Complementary feedings of 60 c.c. of a two-thirds milk formula were given after each nursing. The stools promptly became normal in character and not more frequent than two a day. During the next five weeks the infant gained 1,800 gm., and there were no further symptoms of dyspepsia.

CASE 3.—A girl, born at term, with a birth weight of 3,500 gm., was breast fed entirely for three months, after which time small amounts of cow's milk and oatmeal soup were given. The stools were frequently diarrheal and were mixed with mucus. There was occasional vomiting. At 6 months of age, the infant began to vomit a great deal and the stools became constipated. The infant was admitted to the hospital at the age of 7 months. Her weight at that time was 2,850 gm. The skin was gray and hanging in loose folds. The general picture was that of an extreme degree of athrepsia. The total amount of milk the baby was receiving from the mother averaged 50 gm. daily. Chemical analysis of the milk showed fat, 3 per cent.; protein, 1.2 per cent., and sugar, 6.4 per cent. The infant was given an ordinary diet of milk, vegetables, fruit juices and cereals. The stools became normal in character and there was a gain of 720 gm. during the next three weeks.

## SUMMARY

Partial inanition is a frequent cause of dyspepsia in breast fed infants.

The symptoms of inanition may vary widely. There may be merely weakness, constipation and weight loss, or there may be diarrhea, vomiting and irritability.

The mechanism by which inanition causes the symptoms of dyspepsia is discussed.

# INORGANIC PHOSPHORUS IN THE BLOOD OF THE NEW-BORN

## ITS SEASONAL VARIATION AND ITS RELATION TO RICKETS *

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In the great amount of literature that has been contributed in the past decade to the study of rickets, scant attention has been directed to the consideration of a susceptibility or predilection to the disease. It has been observed in practice that under similar and favorable conditions one of several infants will be more susceptible to the disease than another, or, possibly, that one infant will show evidences of the disorder in a more severe grade than another. What constitutes this difference in susceptibility?

Howland and Kramer [1] have shown that in rickets the inorganic phosphorus content of the serum is lower than in the normal. A low inorganic phosphorus concentration in the serum of some children at birth has been noted, and we have endeavored to see whether we can correlate this decrease in phosphorus with an increase in susceptibility to rickets.

The work was undertaken at Harlem Hospital, which has an active obstetrical service, and the material of this work consists mostly of analytic data on mothers' and infants' blood. Samples of blood were taken from the mother and child at the time of birth. The child's blood was obtained after severing the ligated pulsating cord and permitting the blood to drip into a test tube; that of the mother was taken from a vein. Coagulation was prevented by the use of lithium citrate. Altogether, 1,150 determinations were made; of these, 1,050 were analyzed within twenty-four hours, and 700 within four hours after the withdrawal of the blood. In the time which elapsed between withdrawal of the blood and the analyses, the samples were kept in a

* Received for publication, July 9, 1925.

* From the Harlem Hospital.

* Read before the Section on Diseases of Children at the Seventy-Sixth Annual Session of the American Medical Association, Atlantic City, N. J., May, 1925.

1. Howland, J., and Kramer, B.: Calcium and Phosphorus in the Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

refrigerator at an even temperature immediately under the ice compartment. After the samples were taken out for sub-sampling, they were immediately returned to the refrigerator.

The method of analysis used was that of Tisdall.[2] The analyses were made by a chemist who had made more than 100 similar determinations prior to the project, and his findings were occasionally checked by a second analyst who also checked the standard solutions in use. The average deviation from the mean in duplicate analyses came to ± 0.072 mg. inorganic phosphorus per hundred cubic centimeters. A series of determinations in triplicate gave the results seen in Table 1. The average deviation from the mean is ± 0.027. Three times the probable error for the twelve month period on the infant blood is ± 0.084. We feel justified, therefore, in assuming that no difference between averages of groups is significant unless it exceeds 0.08 mg. inorganic phosphorus per hundred cubic centimeters.

TABLE 1.—*Triplicate Determinations of Inorganic Phosphorus of Blood, Milligrams Per Hundred Cubic Centimeters*

| Mother | | | | Cord | | | |
|---|---|---|---|---|---|---|---|
| | Triplicate | | | | Triplicate | | |
| Case No. | | | | Case No. | | | |
| 1029 | 2.08 | 2.13 | 2.08 | 1030 | 4.06 | 4.20 | 4.11 |
| 1039 | 2.46 | 2.51 | 2.49 | 1040 | 2.82 | 2.80 | 2.80 |
| 1072 | 3.11 | 3.15 | 3.02 | 1073 | 4.33 | 4.30 | 4.32 |
| 1090 | 3.36 | 3.30 | 3.39 | 1091 | 4.16 | 4.18 | 4.20 |
| Extremes, dev. | 0.00-0.08 | | | Average dev. from means | 0.027 | | |

Since inorganic phosphorus of the serum increases on standing at room temperature in contact with the clot, and since the time element could not be ruled out in our analyses, it was thought best to make an inquiry as to any change in the inorganic phosphorus content of the serum samples, even though our specimens were kept at low temperatures. Thirty-one determinations, in which the inorganic phosphorus have been determined within one hour from the time the blood was drawn, were repeated the following day. The results are given in Table 2. It may be noted that there was an increase exceeding 0.08 mg. per hundred cubic centimeters in 61 per cent. of the cases; also, that in about 25 per cent. of the cases the figures obtained the following day were a trifle less than the figures obtained on immediate analysis. Omitting three of the cases, in which the increase was suspiciously great, the average of the differences comes to 0.09 mg. This increment, while only 0.01 mg., is in excess of our fixed limit of significance, and has, therefore, been taken into account.

2. Tisdall, F. F.: J. Biol. Chem. **50**:329 (Feb.) 1922. The advisability of using a more recent method was considered, but the original Tisdall method was strictly adhered to throughout the work for the sake of uniformity in the series of analyses.

In the tabulation of the analytic data by months, on which our study is based, every determination of questionable validity was excluded. Most of the exclusions were made on the basis of time elapsing between sampling and analysis. The full table being too extensive for publication in this journal, a summary by months has been prepared (Table 3). The complete average for the calendar year 1924 is given in Table 4.

The first line in Table 4 gives the "total recorded" cases for the calendar year, 568 mothers and 583 infants. On the next line of the same table are given the "total cases" submitted to detailed study.

TABLE 2.—*Determinations of Inorganic Phosphorus in Whole Blood on Standing Twenty-Four Hours, Milligrams Per Hundred Cubic Centimeters*

| Case No. | Analyzed | | |
|---|---|---|---|
| | Immediate | 24 Hours Later | Difference |
| 0566 | 2.90 | 2.93 | +0.03 |
| 0567 | 3.86 | 3.87 | +0.01 |
| 0569 | 3.98 | 4.07 | +0.09 |
| 0570 | 2.60 | 2.67 | +0.07 |
| 0572 | 3.52 | 3.58 | +0.06 |
| 0573 | 5.18 | 5.18 | 0.00 |
| 0576 | 3.11 | 3.26 | +0.15 |
| 0577 | 3.96 | 4.05 | +0.09 |
| 0580 | 4.56 | 4.40 | −0.16 |
| 0581 | 4.90 | 4.88 | −0.02 |
| 0582 | 4.40 | 4.49 | +0.09 |
| 0636 | 3.45 | 3.32 | −0.13 |
| 0637 | 5.43 | 5.51 | +0.08 |
| 0646 | 2.43 | 2.50 | +0.07 |
| 0647 | 4.17 | 4.06 | −0.11 |
| 0656 | 2.48 | 2.38 | −0.10 |
| 0657 | 4.16 | 4.20 | +0.04 |
| 0666 | 2.57 | 2.68 | +0.13 |
| 0674 | 4.57 | 4.63 | +0.06 |
| 0688 | 4.20 | 4.30 | +0.10 |
| 0689 | 5.60 | 5.43 | −0.17 |
| 0700 | 3.32 | 3.30 | −0.02 |
| 0701 | 4.80 | 4.88 | +0.08 |
| 0708 | 3.59 | 3.59 | 0.00 |
| 0981* | 4.67 | 5.17 | +0.50 |
| 0972* | 4.64 | 5.17 | +0.53 |
| 0967 | 3.54 | 3.72 | +0.18 |
| 0951* | 4.43 | 4.67 | +0.23 |
| 0953 | 3.76 | 3.92 | +0.16 |
| 0959 | 3.58 | 3.71 | +0.13 |
| 0961 | 3.53 | 3.59 | +0.06 |
| | | Average | 0.118 |

* Average dev. omitting these, 0.09.

From this it may be seen that 104 determinations have been excluded, and that the effect of these exclusions on the average inorganic phosphorus of the mother's blood is to lower it by 0.02 mg. and to lower the child's blood by 0.06 mg. per hundred cubic centimeters. The difference between the "total recorded" cases and "total cases" is insignificant, indicating that so far as general averages are concerned, errors in blood allowed to stand twenty-four hours at low temperatures will tend to balance each other. The validity of the data which are here presented may be further judged by the last line in Table 4, which gives the averages of "selected" cases determined as promptly as possible under

the most favorable circumstances. There were 676 such determinations, and the average for these compared with "total recorded" falls within our standard of limitation, which, when compared with the "total cases" used are less by only 0.05 and 0.02 mg. per hundred cubic centimeters. We, therefore, have complete confidence in the analytic data.

TABLE 3.—*Summary of Analytic Data by Months* *

| | January, 1924 | | | | February | | | | March | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No. | M | No. | C | No. | M | No. | C | No. | M | No. | C |
| Total cases | 26 | 3.23 | 26 | 4.76 | 15 | 3.36 | 13 | 4.51 | 28 | 2.91 | 30 | 3.94 |
| Colored | 15 | 3.36 | 17 | 4.93 | 12 | 3.32 | 11 | 4.50 | 22 | 2.96 | 24 | 4.05 |
| White | 9 | 2.99 | 9 | 4.45 | 2 | 3.50 | 2 | 4.56 | 6 | 3.09 | 6 | 3.50 |
| Tropics | 7 | 3.27 | 7 | 4.68 | 3 | 2.97 | 3 | 3.76 | 6 | 2.90 | 6 | 4.43 |
| Selected | 17 | 3.14 | 16 | 4.44 | 9 | 3.26 | 8 | 4.85 | 13 | 2.68 | 14 | 3.54 |
| | **April** | | | | **May** | | | | **June** | | | |
| | No. | M | No. | C | No. | M | No. | C | No. | M | No. | C |
| Total cases | 12 | 3.11 | 12 | 3.61 | 25 | 3.35 | 25 | 3.98 | 70 | 3.08 | 72 | 4.14 |
| Colored | 10 | 3.07 | 10 | 3.29 | 20 | 3.29 | 20 | 3.96 | 51 | 3.09 | 53 | 4.00 |
| White | 2 | 3.34 | 2 | 4.00 | 5 | 3.56 | 5 | 4.05 | 19 | 3.04 | 19 | 4.54 |
| Tropics | 4 | 2.91 | 4 | 3.62 | 7 | 3.57 | 7 | 3.95 | 16 | 3.03 | 17 | 4.14 |
| Selected | 8 | 3.18 | 8 | 3.75 | 10 | 3.53 | 10 | 4.01 | 40 | 3.09 | 40 | 4.17 |
| | **July** | | | | **August** | | | | **September** | | | |
| | No. | M | No. | C | No. | M | No. | C | No. | M | No. | C |
| Total cases | 71 | 3.01 | 84 | 4.18 | 69 | 2.97 | 75 | 4.13 | 36 | 2.95 | 37 | 4.14 |
| Colored | 57 | 3.01 | 68 | 4.24 | 51 | 3.02 | 56 | 4.14 | 31 | 2.91 | 33 | 4.18 |
| White | 14 | 3.01 | 16 | 3.94 | 18 | 2.81 | 19 | 4.09 | 5 | 3.20 | 4 | 3.84 |
| Tropics | 21 | 3.05 | 24 | 4.33 | 24 | 3.04 | 24 | 4.37 | 10 | 2.92 | 10 | 4.22 |
| Selected | 45 | 3.03 | 52 | 4.09 | 33 | 2.99 | 35 | 4.26 | 24 | 2.88 | 25 | 4.07 |
| | **October** | | | | **November** | | | | **December, 1924** | | | |
| | No. | M | No. | C | No. | M | No. | C | No. | M | No. | C |
| Total cases | 37 | 3.16 | 37 | 4.11 | 67 | 3.29 | 66 | 4.22 | 44 | 2.85 | 45 | 3.59 |
| Colored | 38 | 3.15 | 34 | 4.10 | 58 | 3.25 | 57 | 4.20 | 34 | 2.87 | 35 | 3.59 |
| White | 3 | 3.26 | 3 | 4.21 | 9 | 3.74 | 9 | 4.40 | 10 | 2.80 | 10 | 3.67 |
| Tropics | 13 | 3.12 | 13 | 4.26 | 16 | 3.41 | 16 | 4.19 | 9 | 2.94 | 9 | 3.68 |
| Selected | 35 | 2.87 | 27 | 4.10 | 60 | 3.30 | 45 | 4.15 | 44 | 2.85 | 45 | 3.59 |

| | November, 1923 | | | | December, 1923 | | | |
|---|---|---|---|---|---|---|---|---|
| | No. | M | No. | C | No. | M | No. | C |
| Total cases | 10 | 3.83 | 10 | 4.80 | 12 | 2.99 | 13 | 4.35 |
| Colored | 10 | 3.83 | 10 | 4.80 | 11 | 3.00 | 11 | 4.19 |

* In this table, M means milligrams of inorganic phosphorus per hundred cubic centimeters in the blood of the mother, and C, the cord blood of the new-born infant.

TABLE 4.—*Calendar Year, 1924*

| | No. | Mother's Blood | No. | Cord Blood |
|---|---|---|---|---|
| Total recorded | 568 | 3.12 | 583 | 4.18 |
| Total cases | 512 | 3.10 | 535 | 4.13 |
| Colored | 406 | 3.10 | 429 | 4.13 |
| White | 103 | 3.17 | 106 | 4.20 |
| Tropics | 139 | 3.09 | 144 | 4.20 |
| Selected | 344 | 3.05 | 332 | 4.11 |

It was found that the inorganic phosphorus of the infant varies from 1.9 to 7.2 mg. per hundred cubic centimeters. In order to discover what factors may possibly control this wide range of variation, the cases were grouped so as to bring out the import of race, habitat, age, first child or not, twins,[3] season, diet, outdoor sunlight exposure and general climatic condition, including available sunshine and humidity.

3. Questions pertaining to age, first child or not and twins are not considered in this paper.

With regard to race, it will be noted in Table 4 that the negro predominated, constituting nearly 80 per cent. of the cases. These women come from the Harlem district of New York City, and, so far as social and economic conditions are concerned, constitute as homogeneous a group as can possibly be gathered for such a study in which a race factor is also considered. The negro and white may be compared as to race factors without much influence of other variables, with the possible exception of food.

The average inorganic phosphorus for the year is higher in the white mother by 0.07 mg. per hundred cubic centimeters for both mother and infant, but since this falls within our defined limit of significance,

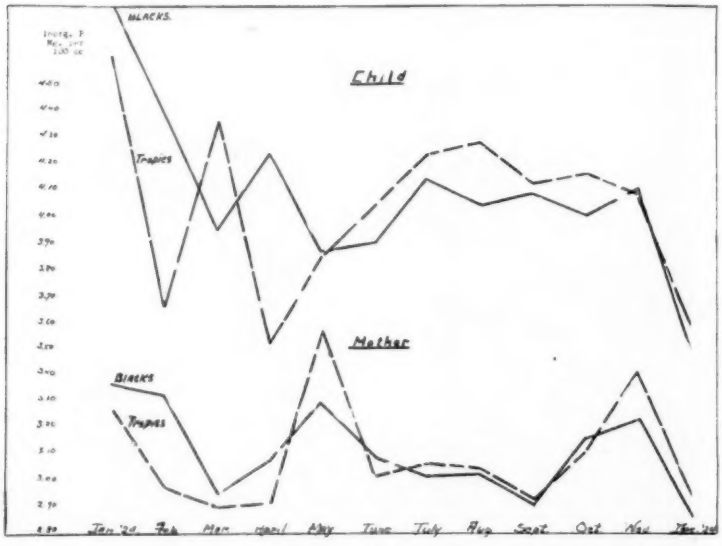


Chart 1.—A comparison of the phosphorus values of native colored mothers and their children and those recently from the tropics.

we may say that a racial factor plays no rôle in determining the amount of inorganic phosphorus in the blood of the new-born.

In Table 4 there is a distribution of cases as to habitat, labeled "tropics," and meaning residence there for some time previous to this study. A survey of case histories showed that 27 per cent. of the mothers came from the West Indies, Porto Rico and the Central American States. It is not possible to tabulate these as to time of residence in New York, but many of them are known to have come here within the year. In this group, the average inorganic phosphorus of mother's and child's blood are in close agreement with the "total cases" (see also Chart 1), and indicate that tropical residence does not

induce in the mother an acquired character which will affect the inorganic phosphorus content of her infant's blood at birth when this occurs in the temperate zone.

AVERAGE INORGANIC PHOSPHORUS

The average inorganic phosphorus content of the blood of the mothers for the year 1924 was 3.10 mg., and for the new-born infant 4.12 mg. per hundred cubic centimeters, mothers ranging from 1.5 to 5.2 mg. and infants from 1.9 to 7.2 mg. In only 5.4 per cent. of the

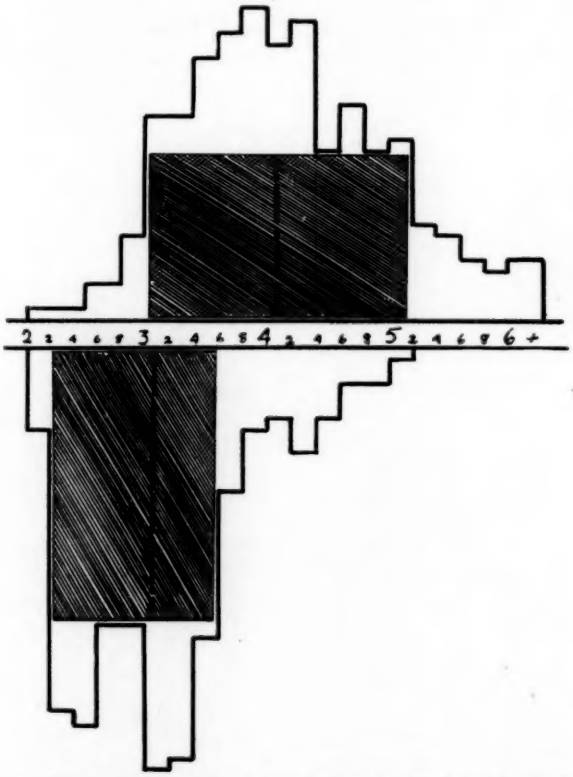


Chart 2.—The frequency of the cases in a population of one hundred.

cases was the mother's blood richer than the infant's blood in inorganic phosphorus. The standard deviation of the inorganic phosphorus in the blood was calculated from 0.2 mg. interval classes, and came to 0.941 mg. for the new-born and 0.643 mg. for the mother. The coefficients of variation are 23 and 25 per cent., respectively. The probable errors are $\pm$ 0.028 mg. for the mother and $\pm$ 0.019 for the infant. In other words, if there are no marked climatic deviations from the last year, nor therapeutic interferences, the chances are 1,310 to 1

that in subsequent years in Harlem the inorganic phosphorus content of the blood in the average woman will lie between 2.95 and 3.15 mg. per hundred cubic centimeters, and that of her new-born child between 3.96 and 4.20 mg.

The frequency of the cases is graphically shown in Chart 2, constructed for the year by distributing the cases by classes with an interval

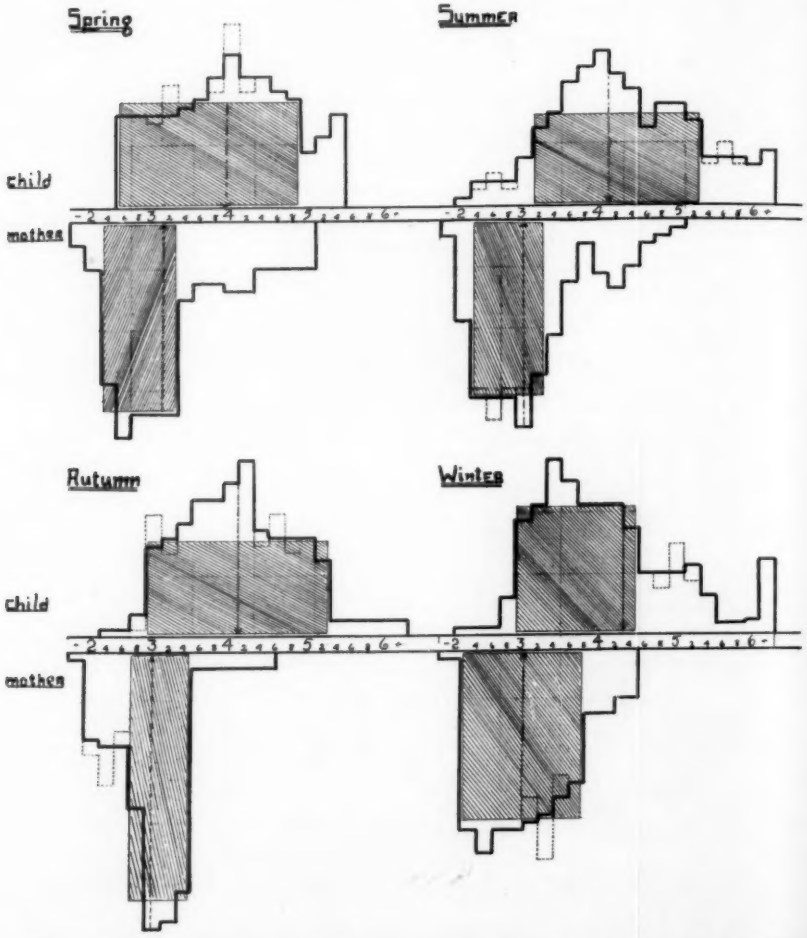


Chart 3.—This represents the frequency polygon for twelve months. The infants are in the upper part and the mothers in the lower part of the drawing

of 0.2 mg. phosphorus, and calculating from this the number of cases which would occur in each of these classes in a population of 100. Each of these cases was then assigned a millimeter square immediately over its appropriate number on the inorganic phosphorus milligram scale. The polygon above the base line pertains to the infant, and that below

to the mother. For the mother, the greatest number of cases comes between 2.2 and 3.6 mg. (77 per cent. of the whole), which is indicated on the polygon by a shaded parallelogram. This is very nearly the range covered by the standard deviation. For the infant the greatest number of cases comes between 3.0 and 5.2 mg. (84 per cent. of the cases). The peak of frequency for the mother is at 3.0 mg., which is below the lower limit of the standard deviation for the infant (3.18 mg.), with a secondary peak at 2.5 mg. The peak of frequency for the infant is at 3.8 mg. In both instances the scattering cases are largely in the higher phosphorus concentration. The inorganic phosphorus content of the mother's blood is much more constant and has a narrower range of variation than that of the infant. This is also indicated in Chart 3, which represents the frequencies by seasons. Although the average inorganic phosphorus content of the mother's blood does not change with the seasons,[4] there is a definite seasonal variation to be noted on examining the frequency polygons. The frequency polygons for the infant are markedly different from those of the mother, indicating much less constant conditions as to the phosphorus content both from season to season and for cases within brief periods of time. The shaded parallelograms of the mother's polygon shifts slightly but perceptibly from season to season. There is a corresponding and more marked shift in the standard deviations in the infant's polygons but the latter lags one season behind the mother's. If the inorganic phosphorus in the blood in the new-born is indicative of susceptibility to rickets, there is in this a suggestion that the causative factors are registering their effect about six to eight weeks prior to the birth of the infant.

The inorganic phosphorus in the infant's blood at birth may naturally be considered as dependent on the food consumed by the mother during gestation.[5] The diets of the mothers were therefore ascertained and were arbitrarily divided into "poor," "fair" and "good." The "poor" diet was composed almost exclusively of starchy foods and sweets, and an excess of tea, coffee or cocoa; the "fair" diet consisted of a large amount of starchy food plus a moderate amount of meat and milk and some of the fresh green vegetables, while the "good" diet was made up of considerable amounts of meats, eggs and cereals and a liberal supply of green vegetables and milk. The data obtained were recalculated on the basis of 100 persons for each group and are given in Table 5.

4. The average inorganic phosphorus in the blood by seasons:

| | Year | Spring | Summer | Fall | Winter |
|---|---|---|---|---|---|
| Cord | 4.12 | 3.8 | 4.2 | 4.2 | 4.5 |
| Mother | 3.10 | 3.1 | 2.9 | 3.1 | 3.1 |

5. Sherman, H. C., and Pappenheimer, A. M.: J. Exper. Med. **34**:189 (Aug.) 1921.

It will be seen from this table that most of the infants showing a high phosphorus at birth were born of mothers subsisting on a good diet, while the low phosphorus figures occur in children of mothers whose diet is considered very poor. This is brought out strikingly by the percentage summary at the bottom of the table.

### INCIDENCE OF RICKETS

It is well known that the incidence of rickets increases in the late winter and spring months, the greatest number of cases occurring in March and April. This has been explained by the lessened amount of

TABLE 5.—*The Relation of Mother's Diet to the Inorganic Phosphorus of Infant's Blood*

| Inorganic Phosphorus in Cord Mg. Per 100 C.c. | 100 Cases Distributed as to Diet | | |
|---|---|---|---|
| | Poor | Fair | Good |
| Over 6 | 4 | 0.5 | 15 |
| 5.6 to 6 | 0 | 0.5 | 7 |
| 5.2 to 5.6 | 1 | 0.0 | 10 |
| 4.8 to 5.2 | 13 | 10 | 13 |
| 4.4 to 4.8 | 4 | 15 | 14 |
| 4.0 to 4.4 | 12 | 17 | 14 |
| 3.6 to 4.0 | 16 | 33 | 14 |
| 3.2 to 3.6 | 29 | 15 | 9 |
| Under 3 | 24 | 7 | 5 |
| Over 4 | 33% | 43% | 72% |
| Under 4 | 67% | 57% | 28% |

TABLE 6.—*Sunlight Hours and Their Relation to Inorganic Phosphorus of Infant's Blood*

| Mg. Inorganic Phosphorus | Over 4 Hours | 2 to 4 Hours | Under 2 Hours |
|---|---|---|---|
| Over 6 | 6.09 | 8.97 | 12.18 |
| 5.4 to 6 | 12.18 | 2.56 | 4.88 |
| 5 to | 13.41 | 14.10 | 8.54 |
| 5.4 | 6.09 | 6.41 | 10.98 |
| 4 to | 15.85 | 18.00 | 13.41 |
| 3.5 | 20.73 | 20.51 | 20.73 |
| 3 to | 21.95 | 16.67 | 13.41 |
| 3 | 3.66 | 12.82 | 15.85 |
| Over 4 | 54% | 50% | 50% |
| Under 4 | 46% | 50% | 50% |

sunlight to which the infant has been exposed in these months. Recognizing sunlight to be a very significant factor in rickets, one would expect that outdoor exposure would be correlated with the phosphorus content of the blood. Many cases were studied, therefore, as to the number of sunlight hours that the mother subjected herself to throughout her pregnancy, that is, the number of hours spent outdoors. The data of this phase of the problem, given in Table 6, do not show any connection between such exposure and the inorganic phosphorus figures obtained from the infant's blood at birth.[6]

6. This is not in accord with the observations of Hutchinson in India. Hutchinson, H. S.: Quart. J. Med. **15**:167 (Jan.) 1922.

We have also taken into account the available sunlight during the period of gestation, as recent studies of sunlight, and particularly of the ultraviolet rays, emphasize the significance of these in physiologic processes.[7] The treatment of rickets by ultraviolet rays and its prompt cure, and the activation of inert material to antirachitic potency,[8] indicate a specificity of these rays in rickets. There is also, as before referred to, a recognized seasonal variation in incidence and severity of rickets which is commonly attributed to these rays.

The data on available sunlight hours used for comparison with the inorganic phosphorus of the infants' blood were secured from a meteorologic survey by the Weather Bureau of the Department of Agriculture[9] for a period of sixteen months beginning with August, 1923, and preceding our study by three months. These two sets of figures are shown in Chart 4. We considered other climatic conditions, and were surprised to find that humidity seemed to play a more important rôle with regard to phosphorus than sunlight. When the relative humidity is plotted against the phosphorus, an even more striking parallelism is revealed. To make this more apparent, the humidity curve is plotted independent of the abscissa for the phosphorus curve, bringing the corresponding peaks in line, that is, moving it forward two months. The curve for the available sunshine hours on this chart has also been shifted forward (one month) so as to bring out the likeness of the curves more clearly. As it became necessary to shift the sunlight curve over a space representing one month and the humidity curve two months, in order to superimpose them it became apparent that the effect of these conditions is registered in the inorganic phosphorus of the infant blood at birth, one month later in sunlight and two months later in humidity.

The inorganic phosphorus curve in Chart 4 reveals interesting variations. The high phosphorus averages for November and December, 1923, and January, 1924, were quite unexpected, but can be explained by the high humidity figures of September, October and November, 1923. The precipitate drop in phosphorus in the following three months coincides with the increasing rickets incidence during this period. The summer average of phosphorus is maintained at an increasingly high level and is followed by the anticipated drop in the month of December, coincident with the drop in the humidity.

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7. Hausser, K. W., and Vahle, W., Grant, J. H., and Gates, F. L.: quoted by Hess, A. F.: The Ultraviolet Rays of the Sun, J. A. M. A. **84**:1033 (April 4) 1925.

8. Hess, A. F.: Tr. Am. Pediat. Soc. **37**:57 (June 7) 1924. Abstr. Am. J. Dis. Child. **28**:517 (Aug.) 1924. Ibid, J. Biol. Chem. **62**:301, 1924. J. A. M. A. **84**:1033 (April 4) 1925. Steenbok, H., and Nelson, M. T.: J. Biol. Chem. **62**: 209 (Nov.) 1924. Steenbok, H., and Daniels, A. L.: Irradiated Foods and Irradiated Organic Compounds, J. A. M. A. **84**:1092 (April 11) 1925.

9. U. S. Dept. Agric. Weather Bureau, Form No. 1030, New York, N. Y

COMMENT

We recognize that rickets is a disease which is primarily a disturbance of the calcium metabolism, manifesting itself in faulty biochemical reactions in the bone tissue, and studies in rickets should take the calcium ion into consideration in the chemical analyses. Our present study is primarily an investigation of the inorganic phosphorus in infant blood and not of rickets. We have, however, made calcium determinations on many samples throughout the twelve months. These have not varied materially from the normal concentration reported by other investigators.[10] These findings are reserved for discussion in the next paper, which will deal more definitely with rickets and the relation of inorganic phosphorus concentration to a prerachitic condition.

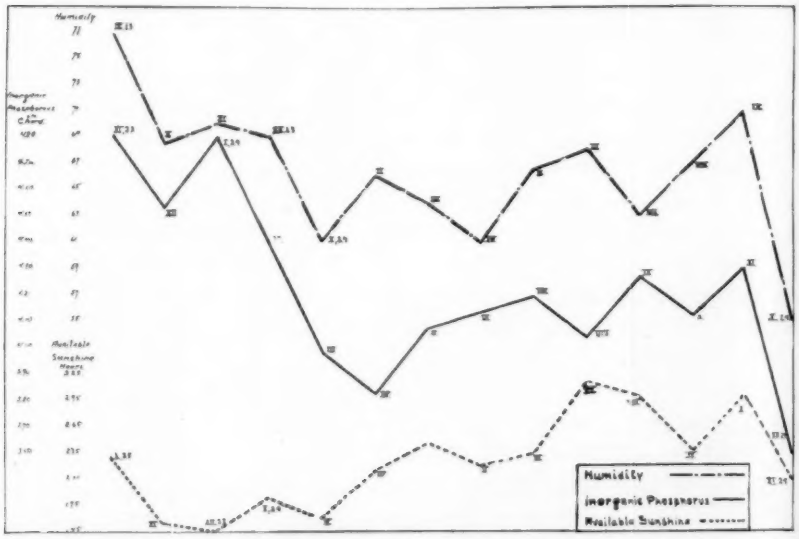


Chart 4.—Relation of humidity, phosphorus and available sunshine by months.

None of the infants used in this study had any clinical signs of rickets at the time of birth,[11] though two-thirds or more would develop this disease if the usual course were not deflected by dietary or radiant treatment.[12] Many of these may be considered in a prerachitic state.[13]

10. Hess, A. F., and Matzner, M. J.: Rickets in Relation to the Inorganic Phosphate and Calcium in Maternal and Fetal Blood, Am. J. Dis. Child. **26**:285 (Sept.) 1923. Denis, W., and King, E. L.: Am. J. Obst. & Gynec. **7**:253 (March) 1924.

11. This is in accord with the work reported by Schmorl, from which he concluded that rickets is not a congenital disease. Schmorl, G.: Egebn. d. inn. Med. u. Kinderh. **13**:403, 1914.

12. The incidence of rickets among the negroes of this neighborhood has been about 80 per cent. of the infants.

13. Prerachitic state: the interval elapsing from the time when the causes for rickets come into effect and the time of a definite rachitic syndrome.

We may suppose that a low inorganic phosphorus content in the blood of the new-born is indicative of this.[14] Where the limits are to be placed for prognosis has still to be determined.

### MOTHER'S DIET

The most striking influence on the phosphorus content of the infant's blood is the general character of the mother's diet. That the diet is not an absolute controlling factor but may be counterbalanced by other influences is obvious from Table 5, in which may be found 4 per cent. of poorly rationed mothers giving birth to infants with the highest phosphorus content, and 5 per cent. of the best fed mothers with infants at the bottom of the scale. This discrepancy is in harmony with Hutchinson's [6] observations in India, to the effect that rickets prevailed among the high caste infants and was rare among those of lower caste. The explanation offered and accepted in the Indian studies is the "purdall" system among the high caste Indians, which deprived them of simple sunlight.

Individual sunlight exposure and the available sunlight in the community were not found to be such obvious causative factors in the inorganic phosphorus of the infant as we were led to expect from the current literature on rickets. The relative humidity, on the other hand, seems strikingly associated with the rise and fall of the average inorganic phosphorus of the infant's blood. This relation between the humidity and blood phosphorus concentration has not hitherto been discovered. This marked influence of humidity does not detract from the importance of sunlight radiation and ultraviolet rays, but brings out another factor which has been overlooked in conjunction with the ultraviolet rays from the sun. The natural inference is that humidity (moisture, precipitation) intensifies the effect of the ultraviolet rays. This is probably effected by increasing the concentration of the rays. The moisture in the atmosphere increases the amount of rays by removing interfering substances. This view is emphatically supported by a physicist, Dobson,[15] who has studied the humidity of the air as a factor in allowing greater transmission of the ultraviolet ray to the earth's surface, and explains this increase in the transmission coefficient of the earth's atmosphere as dependent on the ability of increased humidity and precipitation

14. A study of this phase of the rickets problem, as yet incomplete, has so far not been conclusive, in part due to the lack of cooperation on the part of the mothers, and also due to the fact that in return cases the analyses were on fontanel blood whereas the original determinations were on cord blood. In a previous paper (Am. J. Dis. Child. **29**:611 [May] 1925), the authors have shown that the cord and the superior longitudinal sinus blood are not comparable.

15. Dobson, G. M. D.: Proc. Roy. Soc., London, Sec. A, **104**:252, 1923.

to wash out the dust or particles in the atmosphere, which ordinarily act as a filter to the penetration of the ultraviolet rays to the surface of the earth.

## SUMMARY

1. One thousand four hundred and thirty-nine inorganic phosphorus determinations were made on the blood of mothers and their new-born infants. The investigation extended over a period of fourteen consecutive months, and the data obtained were correlated with the factors causative of rickets.

2. The average of the mother's inorganic phosphorus at delivery was found to be $3.10 \pm 0.019$ mg. per hundred cubic centimeters. The new-born infant's blood averaged $4.12 \pm 0.028$ mg. per hundred cubic centimeters.

3. No significant difference was found between the average inorganic phosphorus of the white and negro mothers or of their infants.

4. The inorganic phosphorus of the blood of the new-born infant was not affected by the previous habitat of the mother (that is, tropics or temperate zone).

5. The time the mother spent out of doors during gestation showed no influence whatever on the inorganic phosphorus of the infants' blood.

6. The diet of the mother was one of the controlling factors of the inorganic phosphorus content of the blood of the new-born infants.

7. A definite seasonal variation of inorganic phosphorus is noted, which is in harmony with the recognized seasonal incidence of rickets.

8. There is a greater variation in the standard deviation in the inorganic phosphorus of the infant's blood than in that of the adult.

9. The curves of available sunlight hours and inorganic phosphorus of the new-born infant are parallel in the latter half of the year, the points of resemblance in the sunlight curve preceding that of the inorganic phosphorus curve by one month.

10. The curve representing relative humidity, a hitherto uncorrelated factor, when compared with the inorganic phosphorus curve of the new-born infant, shows a striking parallelism throughout the year, the points of resemblance preceding the latter by two months.

11. The close relation between relative humidity and the inorganic phosphorus content of the new-born infant's blood is explained as an accentuation of the effects of the ultraviolet rays by removing minute particles which act as a ray filter from the atmosphere.

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# INTRAPERITONEAL TRANSFUSION OF CITRATED BLOOD

## THE EFFECT OF AN INTRAPERITONEALLY PRODUCED PLETHORA ON THE HEMOPOIETIC ACTIVITY OF THE BONE MARROW *

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In a previous paper,[1] an attempt was made to show experimentally the fate of citrated blood when it was injected into the peritoneal cavity. This work was done on a large series of rabbits. Necropsies at various intervals showed that absorption was usually completed in about five hours. In a similar series in which blood studies were made, there was a corresponding increase in hemoglobin and in red blood cells. To show conclusively that the red blood cells actually entered the circulation, pigeons were exsanguinated and the citrated pigeons' blood was injected into the peritoneal cavity of rabbits with the consequent recovery of the foreign, elongated, nucleated pigeons' corpuscles in the rabbits' circulation within fifteen minutes. Subsequently, Ruh and McClelland,[2] and Opitz and Metes [3] have also shown experimentally that when whole, citrated and defibrinated blood is injected into the abdominal cavity, it is absorbed quantitatively into the general circulation with the corresponding blood changes. Other than the foregoing evidence, there was no further experimental proof that the injected blood actually functions.

It is well known that the bone marrow functions at a constant rate to replace the blood cells which are being continually destroyed. It may be assumed that if these cells could be supplied artificially, there would be no need for the formation of new cells, with a consequent temporary decreased activity of the bone marrow.

Robertson,[4] working on this assumption, and using the number of reticulocytes present in the circulation as a guide of bone marrow activity, was able to show experimentally that at the height of an intravenous plethora, the reticulocytes were markedly decreased in the

* Received for publication, July 7, 1925.

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1. Siperstein, D. M., and Sansby, J. Martin: Intraperitoneal Transfusion with Citrated Blood. Experimental Study, Am. J. Dis. Child. **25**:107 (Feb.) 1923.

2. Ruh, H. O., and McClelland, J. E.: Intraperitoneal Transfusion in Infants, Ohio State M. J. **19**:780 (Nov.) 1923.

3. Opitz, Hans, and Metes, Felix: Zur Frage der Intraperitonealen Blutinfusion, Jahrb. f. Kinderh. **107**:269-290 (Dec. 2) 1924.

4. Robertson, O. H.: The Effects of Experimental Plethora on Blood Production, J. Exper. Med. **26**:221, 1917.

general circulation. On the other hand, he found that venesection on a plethoric animal was sufficient to cause a marked bone marrow stimulation which was made evident by the subsequent increase in the number of reticulated cells.

With this idea in mind, it occurred to me that it might be of interest to study the effect of an intraperitoneally-produced plethora on the hemopoietic activity of the bone marrow.

## METHODS

Rabbits served exclusively as recipients and donors. Blood studies were made daily. Hemoglobin estimations were done with the new methods of Sahli; red cells were counted by the usual methods on the Levy counting chamber; the reticulocytes were stained with cresyl blue and examined with an oil immersion lens. The cells which took the stain were counted and the result was expressed in the number of cells per thousand red blood cells. When the count revealed less than 2 per thousand, 3,000 cells were counted and the average taken. Blood for the transfusion was obtained by running a sharp razor across the marginal veins of the ear after topical applications of xylene. The dose for transfusion varied between 30 and 45 c.c. for each animal, and this amount was easily obtained by the procedure mentioned. The blood was collected in 3 per cent. sterile sodium citrate solution, so that after being drawn, it contained 0.3 per cent. sodium citrate. Injection into the peritoneal cavity was best done about 1 inch lateral to the median line of the abdomen, care being taken not to pierce the bladder.

## PRESENTATION OF DATA

Blood studies were made on six apparently healthy rabbits to serve as controls. Complete data and observations are given in Table 1. It will be seen that while the hemoglobin and erythrocyte counts varied slightly, a marked constant fluctuation in the number of reticulocytes occurred. This compares favorably with the findings of Robertson [4] and others, the highest reticulocyte count in the following series being 27, while the lowest was 3. The average hemoglobin estimation of a normal rabbit in this series by the new reaction of Sahli was found to be about from 70 to 75, while the erythrocyte count approached 5,000,000. It will be seen in Table 1 that the animals in Experiments 1 and 5 were anemic at the beginning of the observations. In Experiments 2, 3, 4 and 6, the animals which were normal at the beginning of the observations slowly developed a slight anemia. This may be because the animals were kept inactive in wire cages, and away from their natural environment.

An attempt was then made to produce a plethora in six animals by the intraperitoneal route. Sufficient citrated blood, varying from 30 to 45 c.c., regardless of the weight of the animal, was injected at one time.

TABLE 1.—*Blood Studies of Control Rabbits*

| | Hemoglobin Per Cent. | Red Blood Cells | No. Reticulocytes per 1,000 Red Blood Cells |
|---|---|---|---|
| **Experiment 1—Rabbit—weight, 950 gm.** | | | |
| 1st day | 60 | 4,800,000 | 18 |
| 2d " | 58 | ..... | 27 |
| 3rd " | 56 | 4,900,000 | 22 |
| 4th " | 59 | 4,800,000 | 16 |
| 5th " | 61 | 4,600,000 | 10 |
| 6th " | 61 | 4,700,000 | 6 |
| 7th " | 61 | ..... | 12 |
| 8th " | 62 | 4,800,000 | 13 |
| 9th " | 62 | 4,810,000 | 15 |
| **Experiment 2—Rabbit—weight, 600 gm.** | | | |
| 1st day | 68 | 5,310,000 | 9 |
| 2d " | 70 | 5,750,000 | 16 |
| 3rd " | 70 | 5,500,000 | 4 |
| 4th " | 70 | 5,630,000 | 4 |
| 5th " | 74 | 5,670,000 | 3 |
| 6th " | 70 | 4,880,000 | 7 |
| 7th " | 65 | 4,410,000 | 6 |
| 8th " | 66 | 4,680,000 | 12 |
| 9th " | 64 | ..... | 18 |
| **Experiment 3—Rabbit—weight, 1,650 gm.** | | | |
| 1st day | 80 | 5,650,000 | 20 |
| 2d " | 80 | 5,890,000 | 23 |
| 3rd " | 78 | 5,370,000 | 17 |
| 4th " | 76 | 5,170,000 | 8 |
| 6th " | 75 | 5,250,000 | 11 |
| **Experiment 4—Rabbit—weight, 1,200 gm.** | | | |
| 1st day | 70 | 5,440,000 | 14 |
| 2d " | 67 | 5,360,000 | 9 |
| 3rd " | 67 | 5,100,000 | 13 |
| 4th " | 64 | 4,700,000 | 15 |
| 6th " | 64 | 4,900,000 | 11 |
| **Experiment 5—Rabbit—weight, 1,200 gm.** | | | |
| 1st day | 65 | 4,650,000 | 12 |
| 2d " | 62 | 4,500,000 | 6 |
| 3rd " | 66 | 4,700,000 | 22 |
| 4th " | 64 | 4,650,000 | .. |
| 5th " | 60 | 4,390,000 | 17 |
| 6th " | 58 | 4,100,000 | 20 |
| **Experiment 6—Rabbit—weight, 1,650 gm.** | | | |
| 1st day | 75 | 5,110,000 | 7 |
| 2d " | 71 | 4,950,000 | 8 |
| 3rd " | 72 | 4,840,000 | 6 |
| 4th " | 68 | 4,520,000 | 11 |
| 5th " | 68 | 4,700,000 | 12 |

Data and findings are given in Table 2. It will be noted that in Experiments 7, 8, 9 and 10, the animals responded to the transfusion within forty-eight hours, the degree of plethora attained being variable

TABLE 2.—*Blood Studies of Transfusion Experiments, Showing Marked Production of Plethora in Four Rabbits with a Corresponding Decrease in the Number of Reticulocytes*

| | Hemoglobin Per Cent. | Red Blood Cells | No. Reticulocytes per 1,000 Red Blood Cells |
|---|---|---|---|
| **Experiment 7—Rabbit—weight, 550 gm.** | | | |
| 1st day ..... | 72 | 4,700,000 | 8 |
| 2d " ..... | 73 | 4,750,000 | 13 |
| 30 c.c. citrated blood intraperitoneally | | | |
| 3rd " ..... | 94 | 6,000,000 | 7 |
| 4th " ..... | 96 | 6,600,000 | 6 |
| 5th " ..... | 100 | 6,500,000 | 5 |
| 6th " ..... | 97 | 6,400,000 | 1 |
| 7th " ..... | 92 | 6,200,000 | 1–0 |
| 8th " ..... | 93 | 6,240,000 | 1–0 |
| 10th " ..... | 95 | 6,700,000 | 0 |
| **Experiment 8—Rabbit—weight, 550 gm.** | | | |
| 1st day ..... | 70 | 5,920,000 | 14 |
| 40 c.c. citrated blood intraperitoneally | | | |
| 2d " ..... | 82 | 6,100,000 | 6 |
| 3rd " ..... | 100 | 7,750,000 | 5 |
| 4th " ..... | 110 | 7,640,000 | 7 |
| 5th " ..... | 110 | 8,210,000 | 3 |
| 6th " ..... | 110 | ..... | 1 |
| 7th " ..... | 100 | 7,350,000 | 0 |
| 8th " ..... | 95 | 6,980,000 | 1–0 |
| 9th " ..... | 90 | 6,950,000 | 1 |
| **Experiment 9—Rabbit—weight, 1,300 gm.** | | | |
| 1st day ..... | 70 | 5,280,000 | 20 |
| 45 c.c. citrated blood intraperitoneally | | | |
| 2d " ..... | 75 | 6,010,000 | 18 |
| 3rd " ..... | 76 | 6,010,000 | 13 |
| 4th " ..... | 92 | 6,850,000 | 9 |
| 5th " ..... | 92 | 6,540,000 | 3 |
| 6th " ..... | 94 | ..... | 4 |
| 7th " ..... | 95 | 6,410,000 | 2 |
| 8th " ..... | 90 | 6,050,000 | 1–0 |
| 9th " ..... | 88 | 5,950,000 | 2 |
| 10th " ..... | 90 | 6,040,000 | 1 |
| 11th " ..... | 90 | 6,100,000 | 1 |
| **Experiment 10—Rabbit—weight, 1,500 gm.** | | | |
| 1st day ..... | 70 | 5,870,000 | 14 |
| 45 c.c. citrated blood intraperitoneally | | | |
| 2d " ..... | 75 | 6,060,000 | 5 |
| 3rd " ..... | 85 | 6,700,000 | 10 |
| 4th " ..... | 98 | 6,880,000 | 7 |
| 5th " ..... | 98 | 6,700,000 | 2 |
| 7th " ..... | 100 | 6,940,000 | 2 |
| 8th " ..... | 94 | 6,640,000 | 2 |
| 9th " ..... | 95 | 6,600,000 | 1 |
| 10th " ..... | 93 | 6,610,000 | 1 |

in each animal. Following the establishment of the plethora, the reticulocytes began slowly to decrease in number until there were only from 0 to 2 per thousand red blood cells, at which level they remained until the end of the experiment (Charts 1 and 2). At necropsy, eleven days after the transfusion, there was no evidence of blood, clots, nor adhesions in the abdominal cavity.

In Experiments 11 and 12, it appears that the animals were apparently anemic at the beginning of the experiment.

TABLE 2.—*Continued*

| | Hemoglobin Per Cent. | Red Blood Cells | No. Reticulocytes per 1,000 Red Blood Cells |
|---|---|---|---|
| **Experiment 11—Rabbit—weight, 1,000 gm.** | | | |
| 1st day ..... | 61 | ..... | 6 |
| 2d " ..... | 60 | ..... | 12 |
| 3rd " ..... | 62 | ..... | 10 |
| 4th " ..... | 61 | ..... | 15 |
| 40 c.c. citrated blood intraperitoneally | | | |
| 5th " ..... | 75 | ..... | 13 |
| 6th " ..... | 80 | ..... | 5 |
| 7th " ..... | 78 | ..... | 4 |
| 8th " ..... | 80 | ..... | 7 |
| 9th " ..... | 78 | ..... | 11 |
| 10th " ..... | 70 | ..... | 9 |
| 11th " ..... | 70 | ..... | 12 |
| **Experiment 12—Rabbit—weight, 1,150 gm.** | | | |
| 1st day ..... | 63 | 4,750,000 | 19 |
| 2d " ..... | 60 | 4,750,000 | 17 |
| 3rd " ..... | 60 | 4,700,000 | 23 |
| 4th " ..... | 60 | 4,300,000 | 27 |
| 5th " ..... | 62 | 4,360,000 | 28 |
| 6th " ..... | 64 | ..... | 18 |
| 7th " ..... | 64 | 4,650,000 | 23 |
| 35 c.c. citrated blood intraperitoneally | | | |
| 8th " ..... | 62 | 4,100,000 | 20 |
| 9th " ..... | 61 | 4,280,000 | 16 |
| 10th " ..... | 68 | 5,200,000 | 6 |
| 11th ' ..... | 70 | ..... | 3 |
| 12th " ..... | 68 | 5,100,000 | .. |
| 13th " ..... | 60 | ..... | 9 |

The animal in Experiment 11 responded to the transfusion very poorly. The blood findings would indicate that the transfusion did not cause the production of a plethora but only corrected the anemia. The reticulocytes also remained within normal limits. At necropsy six days after transfusion, the abdominal cavity was free from blood and there were no clots or adhesions.

In Experiment 12, it will be seen from the data that the transfusion had very little effect. There was a tendency for the blood values to return to normal only to fall again. At necropsy six days after the transfusion, the abdominal cavity contained a concentrated bloody fluid.

Examination of this fluid showed the presence of normal, unchanged red blood cells. There was apparently very little absorption of blood in this case.

## COMMENT

The reticulocyte, being a normal constituent of the blood, is present in amounts varying from 5 to 20 per thousand for human beings and somewhat higher for rabbits. An increase in the number of reticulocytes constitutes the earliest circulatory evidence of increased hemopoietic function of the bone marrow. When, however, the bone marrow for any reason is inhibited, as in disease and experimental intravenous

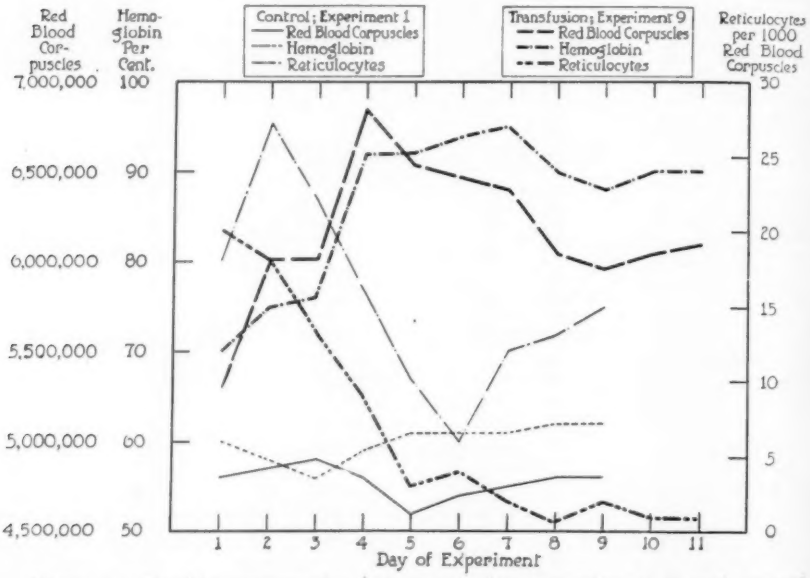


Chart 1.—Graphic presentation of transfusion Experiment 9 and control Experiment 1. In Experiment 9, 45 c.c. of citrate blood was injected into the peritoneal cavity.

plethora, the tendency for the reticulated cells is to decrease in number and in some cases to disappear entirely temporarily. When the stimulation is very slight, the enumeration of the reticulocyte serves as the most sensitive and reliable guide for detecting all degrees of bone marrow activity. Its significance is attested by the following investigators: Robertson,[4] Key,[5] Cunningham,[6] Vogel and McCurdy,[7] and others.

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5. Key, J. A.: Studies on Erythrocytes with Special Reference to Reticulum, Polychromatophilia and Mitochondria, Arch. Int. Med. **28**:511 (Nov.) 1921.

6. Cunningham, T. D.: Method for Permanent Staining of Reticulated Red Cells, Arch. Int. Med. **26**:405 (Oct.) 1920.

7. Vogel, K. M., and McCurdy, U. F.: Blood Transfusion and Regeneration in Pernicious Anemia, Arch. Int. Med. **12**:707, 1913.

It has already been shown experimentally [4] that after an intravenous plethora, the reticulocytes of the blood decrease in number and in some instances may remain absent temporarily. This is attributed to the fact that the artificially introduced red blood cells compensate for the red blood cells which are normally being destroyed. Consequently there is no need for the formation of new erythrocytes. So long as this artificial replacement of erythrocytes continues, the bone marrow

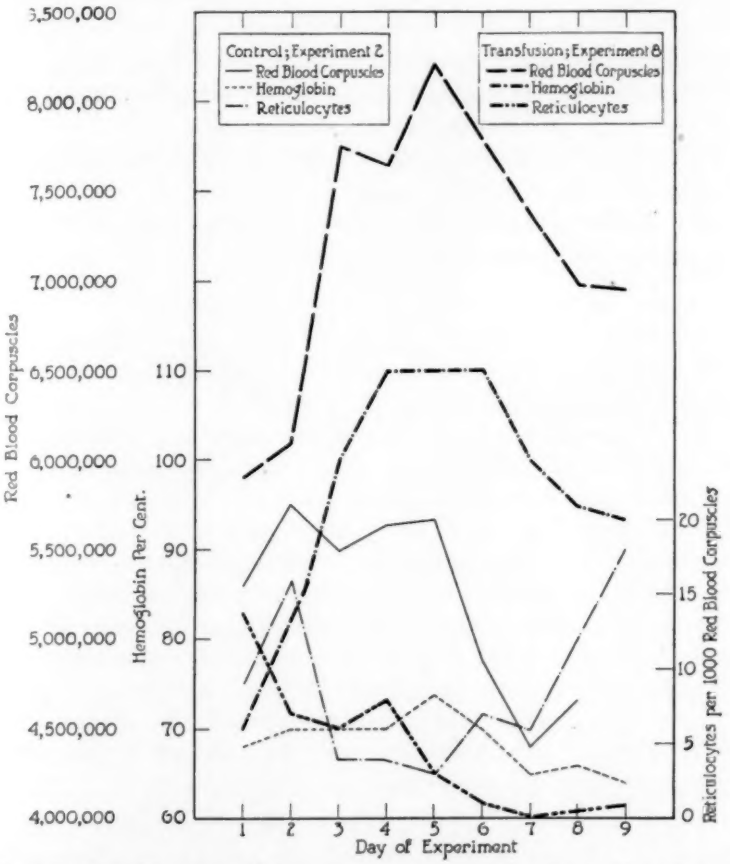


Chart 2.—Graphic presentation of transfusion Experiment 8 and control Experiment 2. In Experiment 8, 40 c.c. of citrated blood was injected into the peritoneal cavity.

assumes a state of decreased activity which is made evident by the temporary disappearance or reduction in the number of reticulocytes in the circulating blood.

If the intraperitoneal injection of blood is to be considered a true transfusion, and if the red blood cells so injected are in a functioning state, a plethora produced by the intraperitoneal route ought to have the

same effect as the intravenous plethora does on the bone marrow. From these experiments it can be seen that in four out of six animals, the intraperitoneally produced plethora caused the reticulocytes to decrease in number and in some instances to disappear entirely. This would suggest the similarity of behavior of the blood introduced indirectly into the circulation through the abdominal cavity and that introduced directly as in intravenous transfusions.

## CONCLUSION

An intraperitoneally produced plethora of citrated blood has an inhibitory effect on the hemopoietic function of the bone marrow, similar in nature to that produced by the intravenous route.

This substantiates further the viability of the red blood cells introduced by intraperitoneal transfusion.

Care should be used in the selection of donor and recipient when using rabbits for intraperitoneal transfusion.

# UROBILIN EXCRETION IN CHILDREN WITH ANEMIA*

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Urobilin excretion in the stools is generally considered one of the few methods at hand of determining the presence or absence of blood destruction in patients in whom the blood count and hemoglobin are low, and in whom it is important to find out whether there is an actual destruction of red cells after they are formed or a lack of production of red cells. Pearce, Krumbhaar and Frazier[1] mention it as being one of the valuable methods for determining the state of the hematopoietic system in adults, used in conjunction with smears to determine the presence or absence of regeneration forms and stippled cells, and also in conjunction with fragility tests. It has been used for diagnosis in various kinds of anemia, in splenomegalies, in purpuras and in hemolytic jaundice.

There is considerable variation between the urobilin excretion of adults and of children. Wilbur and Addis found the range from 3,307 to 8,737 urobilin units in adults. Denzer and Merritt[2] found the range in infants under 1 year from 0 to 119 units, and Bass, Denzer and Herman found it to be from 147 to 1,345 units in normal children from 18 months to 11 years. Wilbur and Addis[3] found that in one case of pernicious anemia in an adult, the urobilin units ranged from 22,000 to 24,000 units. In Pearce and Krumbhaar's case of pernicious anemia, the number of urobilin units was 18,300, and after splenectomy it varied from 16,000 to 23,000. In a patient with congenital hemolytic jaundice, these writers found the urobilin units to be 71,250 before splenectomy, and 7,954 after splenectomy. Bass, Denzer and Herman,[4] in their study of twenty-one children, ranging in age from 6 to 10 years, suffering from various forms of anemia and diseases of the spleen and hematopoietic system, found their highest values to be as follows:

Congenital hemolytic jaundice, 4,862 urobilin units; trichinosis, 1,174 units; purpura hemorrhagica, 1,070 units, and a splenomegaly of unknown origin, 2,233 units.

## METHOD

By "urobilin" is meant the sum of the urobilin and urobilinogen excreted in the stools. The method employed in the present series of

* Received for publication, July 9, 1925.

* From the Children's Medical Division, Bellevue Hospital, and the Department of Diseases of Children, Columbia University.

1. Pearce, R. M.; Krumbhaar, E. B., and Frazier, C. H.: The Spleen and Anemia, Philadelphia, J. B. Lippincott & Company, 1918.

2. Denzer, B. S., and Merritt, K. K.: Studies on Anemia in Infancy, Am. J. Dis. Child. **27**:297 (April) 1924.

3. Wilbur and Addis: J. M. Sc. **13**:225, 1914.

4. Bass, M. H.; Denzer, B. S., and Herman, H.: Urobilin Secretion in the Anemias of Infants and Children, **27**:433 (May) 1924.

cases was that of Wilbur and Addis. All the stools were collected for a twenty-four hour period, for five to six consecutive days. The twenty-four hour total was ground up in a mortar, with enough water to make a uniform suspension. To 25 c.c. of this suspension, 75 c.c. of acid alcohol was added, and the mixture was shaken for one-half hour in a shaking machine. To this was added an equal quantity (100 c.c.) of a saturated solution of zinc acetate in alcohol, and the mixture was again shaken.

To 20 c.c. of the filtrate, 2 c.c. of Ehrlich's reagent was added. This mixture was kept in the dark over night; it was then examined with a spectroscope by daylight. The urobilinogen band lies between the red and yellow bands in the spectrum, and the urobilin band lies between the yellow and blue bands. The solution was diluted with 60 per cent. alcohol until both bands disappeared. From the number of cubic centimeters required to make the bands disappear, together with the amounts of acid alcohol and zinc acetate added to the original suspension, can be calculated the number of dilutions necessary to make the urobilin and urobilinogen bands disappear. The calculation is made thus:

$$\frac{\text{Number of cubic centimeters to which stool is diluted}}{25} \times 8 \times \left\{ \begin{array}{c} \text{Amount necessary for disappearance of urobilinogen band} \\ + \\ \text{Amount necessary for disappearance of urobilin band} \end{array} \right\} = \text{Units of "urobilin"}$$

The number obtained in this manner is used to express roughly the amount of blood destruction present.

This method was used on fourteen children at Bellevue Hospital, in whom the red counts and hemoglobin were below normal, except one whose liver was very much enlarged, but whose red count and hemoglobin were practically normal. Five normal children were studied, their ages ranging from 1½ to 10 years. Their hemoglobin was over 80, and their red cells were over 4,500,000. The urobilin units ranged from 116 to 680. There was not a consistent increase in the urobilin units according to age. Of the pathologic cases studied, the one which showed the highest urobilin value—848 units—was that of a boy with cirrhosis of the liver (the history suggested the possibility of an alcoholic cirrhosis). The average for his age would be about 204 units. This figure was obtained on his second admission, when the red count was 2,600,000, and the hemoglobin 45 per cent. On his first admission, when the urobilin units were 556, the red count was 4,480,000 and the hemoglobin 80 per cent. Although there is not a striking difference between the urobilin units, the increase found in the second admission is evidently a reflection of the blood destruction going on, as also shown by the red cells and hemoglobin. It is quite definitely higher than the figures obtained in normal children of approximately the same age, that

is, 145 and 263 units. One child, aged 3, with malaria, had 434 urobilin units, which is slightly above the average for the age. Another child, aged 4 years, with a sarcoma of the orbit, had 512 units, which is also somewhat above the average for the age. A boy, aged 7, with secondary anemia, had 672 units, the average being 204 units. There were no strikingly high figures in this series. Several writers are agreed that the highest figures are to be found in congenital hemolytic jaundice. Pearce and Krumbhaar found the urobilin units to be 71,250 in an adult with congenital hemolytic jaundice. Bass, Denzer and Herman

TABLE 1.—*Urobilin Excretion in Normal Children*

| Names | Age, Years | Hemoglobin, % | Red Blood Cells | Days Observed | Units Urobilin |
|---|---|---|---|---|---|
| J. M. | 1½ | 80 | 4,560,000 | 2 | 388 |
| T. M. | 2 | 84 | 4,688,000 | 4 | 116 |
| A. P. | 7 | 82 | 5,152,000 | 5 | 145 |
| J. K. | 7 | 105 | 4,792,000 | 6 | 263 |
| G. P. | 10 | 88 | ? | 2 | 680 |

TABLE 2.—*Urobilin Excretion in Children with Anemia*

| Name | Age, Years | Diagnosis | Hemoglobin, per Cent. | Red Blood Cells | No. Days Observed | Urobilin Units |
|---|---|---|---|---|---|---|
| M. W. | 10½ | Banti's disease | 42.4 | 2,150,000 | 6 | 298 |
| H. S. | 7 mo. | Secondary anemia (nutritional?) | 27.6 | 3,800,000 | 6 | 6 |
| T. | 1 | Secondary anemia, idiocy | 33 | 3,272,000 | 6 | 26 |
| F. K. | 4 | Pyelitis, secondary anemia | 54.6 | 2,360,000 | 6 | 292 |
| J. R. | 6 | Cirrhosis (alcoholic?) idiocy | 1st admission, 80 | 4,480,000 | 6 | 556 |
| | | | 2d admission, 45 | 2,744,000 | 6 | 848 |
| C. M. | 4 | Sarcoma of liver | 5.6 | 2,600,000 | 7 | 425 |
| L. P. | 9 mo. | Lobar pneumonia, secondary anemia | 15 | 1,530,000 | 5 | 6 |
| S. C. | 1 | Rickets, secondary anemia | 25 | 3,076,000 | 6 | 103 |
| J. K. | 7 | Secondary anemia | 12 | 2,100,000 | 6 | 672* |
| M. H. | 6 | Secondary anemia following tubercular meningitis | 71 | 3,632,000 | 6 | 149 |
| G. E. | 15 mo. | Secondary anemia | 30 | 1,448,000 | 6 | 128 |
| M. T. | 3 | Malaria | ? | ? | 6 | 434 |
| J. S. | 6½ | Tubercular peritonitis | 70 | 4,100,000 | 6 | 101 |
| B. C. | 6 | Purpura | 30 | 1,144,000 | 6 | 138 |
| A. C. | 4 | Sarcoma of orbit | ? | ? | 2 | 512 |

* Transfusions were given between the first and second determinations.

found their highest values, 4,862 units, in a boy, aged 6 years, with congenital hemolytic jaundice.

## SUMMARY

From this series of cases, in which the urobilin values are markedly lower than in the series of Bass, Denzer and Herman, it does not seem that the estimation of urobilin in children is as valuable a method as it is in adults, since there is often no marked increase when the clinical picture and blood findings would make the presence of blood destruction probable. There is little consistency either in the type of anemia or in the age of the child, as to the urobilin findings.

# EXTREME LEUKOCYTOSES IN PERTUSSIS

## A SURVEY OF THE LITERATURE AND REPORT OF TWO CASES *

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The marked leukocytosis occurring in pertussis is generally recognized and frequently used in the diagnosis of mild and obscure cases of the disease. Fröhlich,[1] in 1897, was probably the first to draw attention to its occurrence.[2] He reports a constant high leukocyte count in about eighty cases studied during an epidemic of pertussis in Breslau.

Fröhlich's observation was shortly afterward confirmed in the classical investigation of Meunier.[3] The latter made repeated blood counts on 104 cases. The average of his maximum counts was 27,800 per cubic millimeter, and he obtained 23,700 as the general average at the height of the disease. Several leukocyte counts exceeded 40,000 and the highest noted was one of 51,150.

The reports of counts of 80,000 and more in this disease are relatively few in the literature, and but eight were found which surpassed 100,000. This paper was undertaken to emphasize these extraordinarily high numbers which may occur, and to report two cases which might be confused with acute leukemia.

### REVIEW OF THE LITERATURE

The highest leukocytoses are usually met with in pertussis-pneumonia. Cabot[4] reports two such cases occurring in The Massachusetts General Hospital. The first case was that of a child, aged 6 years, who had a white blood count of 94,600, of which 69 per cent. were lymphocytes. The count became normal during convalescence and the child made an uneventful recovery. The second case was that of a baby, aged 15 months, whose paroxysms began four days before admission. The leukocytes numbered 103,000 and 64.5 per cent. of them were lymphocytes. On the third day the count had reached 185,000. The red blood cells were normal and no nucleated varieties

* Received for publication, July 14, 1925.

* From the Division of Pediatrics, Stanford University Medical School.

1. Fröhlich, J.: Beitrag zur Pathologie des Keuchhustens, Jahrb. f. Kinderh. **44**:53, 1897.

2. It may have been mentioned by Stiénon, Jour. de méd. de chirurg. et de Pharm. **4**:1, 1895.

3. Meunier, H.: De la leucocytose dans la coqueluche, Arch. de méd. d. enf. **1**:193, 1898.

4. Cabot, R. C.: Clinical Examination of the Blood, New York, William Wood & Company, 1904.

were seen. The patient subsequently died and, while no necropsy was performed, it had been noted that the spleen and lymph glands were not enlarged.

Cabot also refers to a case of "bronchopneumonia" with paroxysmal cough and cyanosis in a child, aged 22 months, reported by Stevens.[5] This, he thinks, was pertussis pneumonia. A maximum leukocytosis of 227,810; polymorphonuclears, 33.6 per cent. and lymphocytes, 50.2 per cent., was observed. The spleen was not palpable. This patient also died and no necropsy was made.

Crombie[6] reports counts of 180,000, 233,000 and 225,000 obtained on different occasions in an infant, aged 20 months. The patient was admitted to the hospital with convulsions in the second week of an attack of pertussis. Another of his patients was a girl, aged 3 years, who had had the disease for six weeks. When first seen, the white blood count was 120,000, polymorphonuclears 31 per cent., and lymphocytes 67 per cent. Later counts were one of 113,600 and another of 141,000. Both of these patients showed no abnormal physical signs on entry but bronchopneumonia was found at necropsy. The bone marrow was examined and found abnormally vascular but otherwise normal. The lymph glands were congested with blood and of a deep red color on section. There was nothing in their appearance to suggest leukemia.

Reiche[7] mentions a case of pertussis complicated by influenza with a leukocytosis of 172,000; polymorphonuclears 56.3 per cent.; lymphocytes 43.6 per cent. The patient was seen at an early stage but the details are not given.

Two high counts were noted in the series of 100 cases reported by Churchill.[8] One, of 112,000, occurred at the height of a severe attack of pertussis in a child, aged 4 years. The other was 89,000. No mention is made of any complication in the course of either case.

Austrian[9] reports in detail the case of a colored child, aged 4. The patient had bronchopneumonia when admitted to the hospital in the second week of illness. The history of an unproductive cough, occurring in nocturnal paroxysms and at times so severe as to induce vomiting, perhaps justifies a suspicion of pertussis as the primary disease. The leukocytes numbered 130,000 on admission and attained a maximum of 206,000 the next day. The differential count showed 52 per cent.

5. Steven, J. L.: Acute Infantile Bronchopneumonia, Brit. M. J. **2**:791, 1902.
6. Crombie, J. F.: The Leucocytosis of Whooping-Cough, with Analysis of One Hundred and Twelve Cases, Edinburgh M. J. **1**:222, 1908.
7. Reiche, F.: Keuchhusten und Influenza, München. med. Wchnschr. **67**: 1352, 1920.
8. Churchill, F. S.: Diagnostic Value of the Leucocyte Formula in Pertussis, J. A. M. A. **46**:1506 (May 19) 1906.
9. Austrian, C. R.: Hyperleucocytosis of High Grade in Bronchopneumonia in a Child, Bull. Johns Hopkins Hosp. **22**:296, 1911.

polymorphonuclears, 24 per cent. lymphocytes, 0.6 per cent. large mononuclears, 4 per cent. eosinophils, 3 per cent. transitionals and 12 per cent. myelocytes. There were a few unclassified white cells. The red blood cells were essentially normal in number and in appearance. A few normoblasts but no megaloblasts were noted. The patient died of acute mastoiditis and sinus thrombosis. The necropsy showed no evidence of leukemia.

In a survey of the literature, Austrian found leukocytoses in excess of 100,000 reported in the following conditions: multiple carcinoma; appendicitis gangrenosa complicated by hemorrhage from a duodenal ulcer; lobar pneumonia and splenohepatic cirrhosis.

Bourne and Scott's [10] case is a relatively recent one. A girl, aged 21 months, had typical pertussis with bronchopneumonia. The paroxysms had been of twelve days duration. The white blood count was found to be 176,000; lymphocytes 66 per cent. The leukocytosis was less than 30,000 on dismissal some five weeks later.

## REPORT OF TWO ADDITIONAL CASES

CASE 1.—K. T., a boy, aged 4 years, Japanese, first came under observation April 4, 1925. There had been known contact between this patient and a child with pertussis four weeks previously. The boy's illness was of two weeks duration and had begun with a cough. It became progressively worse and definitely paroxysmal but was unaccompanied by a whoop. There had been severe and increasing prostration for a period of three or four days.

The patient appeared apathetic and there was marked increase in the number of respirations. The physical examination, excepting the chest, was negative. Dulness was demonstrable in the right lower axilla and here râles were numerous. Bronchial breathing was absent. A blood count was made April 8, and the leukocytes were found to number 192,000 per cubic centimeter; polymorphonuclears, 28 per cent.; lymphocytes, 61 per cent. The following day the count was 140,000.

The patient was admitted to Lane Hospital, April 11, one week later. The signs of bronchopneumonia were then well marked and the roentgenogram showed increase in the bronchial markings and an area of heavy density in the right lower lobe. There was extreme dyspnea with cyanosis of such a marked degree as to require the constant administration of oxygen. The temperature fluctuated between 100 and 103.6 F. No enlargement of the spleen or lymph glands was ever demonstrable.

A blood examination on April 13 showed red blood cells, 4,870,000 and leukocytes, 116,000. The polymorphonuclears were 56 per cent. and the lymphocytes were 43 per cent. The percentage of hemoglobin was 57 per cent. (Sahli). Blood smears were examined by Dr. Harry Wyckoff, who found many nucleated red cells, normoblasts and a small percentage of megaloblasts and myelocytes. The blood platelets were normal in number, 340,000 per cubic millimeter.

A provisional diagnosis of acute leukemia was made on these findings, despite the normal platelet count. Transfusion was decided on as a palliative. The intravenous method was partially successful and 25 c.c. of whole blood was thus administered. Later, the same day, 50 c.c. of citrated blood was injected intraperitoneally.

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10. Bourne, G., and Scott, J. M.: Pertussis with a Leukocytosis of 176,000, Brit. M. J. **1**:386, 1922.

The following day the patient appeared somewhat improved. The number of leukocytes had dropped to 82,000 with the polymorphonuclears and lymphocytes in equal numbers.

On April 15, 50 c.c. more of citrated blood was given intraperitoneally. The patient failed to improve, however, and died early the following day before another blood count was made. There was no necropsy.

CASE 2.—L. D., a boy, aged 8 months, was first seen April 10, 1925, in the paroxysmal stage of severe pertussis apparently contracted from his brother. Vomiting was marked. Routine symptomatic treatment was ordered. There were no abnormal physical findings.

On April 16, in response to an emergency call, the patient was again visited. At this time there was marked prostration, extreme cyanosis and very rapid breathing. Hyperpyrexia and general muscular twitching were present. Examination of the chest elicited signs of a diffuse bronchopneumonia, impaired resonance, many moist râles and small scattered areas posteriorly, in which the breath sounds were increased in intensity. The abdomen was slightly distended but in other respects was normal. Immediate hospitalization was advised and accepted.

Shortly after the infant was admitted to the hospital, the temperature (rectal) rose to 105.2 F. and almost continuous clonic convulsions set in. These symptoms lasted but a few hours and the patient went on to an uncomplicated recovery.

*Blood Counts in Case 2*

| Date | Red Blood Cells per C.Mm. | White Blood Cells per C.Mm. | Polymorphonuclears, per Cent. | Lymphocytes, per Cent. |
|---|---|---|---|---|
| April 17 | ..... | 162,500 | 25 | 74 |
| 20 | ..... | 157,000 | 52 | 44 |
| 23 | ..... | 137,000 | 42 | 56 |
| 27 | ..... | 48,500 | 45 | 53 |
| 30 | ..... | 39,000 | 47 | 51 |
| May 1 | ..... | 28,650 | 30 | 68 |
| 2 | ..... | 29,000 | 36 | 63 |
| 3 | ..... | 22,750 | 35 | 62 |
| 4 | ..... | 27,750 | 57 | 42 |
| 22 | 4,220,000 | 9,600 | 43 | 51 |

The temperature which was remittent, ranging from 100 to 104 F., subsided by lysis and became normal by the fourteenth day of the pneumonia. The paroxysmal cough lasted well into convalescence.

The blood counts in this case are tabulated.

A blood platelet count was not made. Blood smears, taken at the beginning of the pneumonia, showed abnormal cells as in the preceding case. The most striking reduction in the number of leukocytes, between May 23 and 27, was coincident with the greatest clinical improvement.

On April 30, May 2 and 4, after the subsidence of the fever, the chest was exposed to small doses of roentgen ray. These had no appreciable effect on the leukocytosis but apparently effected an increase in the number of polymorphonuclear cells. Roentgenograms were taken for comparison before and after this course of treatment. They failed to show any change in the size of the tracheobronchial lymph glands.

The patient has been seen several times since he left the hospital over a month ago and remains well.

## THEORIES CONCERNING THE CAUSE OF THE LEUKOCYTOSES

Various explanations are advanced to explain the lymphemia observed. Meunier thinks it is in part due to the extreme congestion of the tracheobronchial lymph glands, and cites as evidence the remarkable multiplication of the lymphogenous cells. Cabot agrees with this view

but Crombie thinks that, while the lymphocytosis may be secondary to such glandular stimulation, it denotes a positive chemotactic action.

Gulland and Goodall [11] likewise believe in a chemotactic action, but think that the bronchial lymph glands could not possibly supply such large numbers of lymphocytes as are present. They point out that the polymorphonuclear cells, as well as the lymphocytes, are greatly increased in numbers, though not proportionately so. They conclude that both increases are derived from the bone marrow.

Reiche explains his high count on a basis of the mixed infection, and Bourne and Scott think such an explanation might apply to their case which occurred during an influenza epidemic.

Hess [12] attempted to obtain the explanation by making blood counts immediately after paroxysms and after intervals of quiet. The results of his work lead him to conclude that the lymphocytosis is a secondary mechanical effect, that is, the paroxysms, by increasing intra-abdominal pressure, squeeze lymphocytes out from the spleen and thoracic duct into the circulation.

The presence of abnormal cells in the smears from several of these cases, as in ours, support the belief of Gulland and Goodall that these enormous increases in the white blood cells are myelogenous. Twelve per cent. myelocytes were reported in Austrian's case, and these cells were found in both of our cases. Nucleated red cells and megaloblasts were also present.

All of these cells appear in the recent tabulation of Lucas and Hoobler [13] as accepted evidence of regeneration in blood cells. Their presence is indicative of increased functional activity in the bone marrow —whatever may be the initiating cause.

## CONCLUSION

White blood counts exceeding 100,000 may represent extreme leukocytoses and should not be confused with acute leukemia. In the presence of such large numbers, a careful investigation should be made to rule out pertussis as the primary disease.

The number of blood platelets, nearly always greatly reduced in acute leukemia, is of value in making the differential diagnosis.

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11. Gulland, G. L., and Goodall, A.: The Blood, London, W. Green & Sons, 1912.

12. Hess, R.: Zur Keuchenlymphocytose, Ztschr. f. Kinderh. **27**:117, 1920.

13. Lucas, W. P., and Hoobler, H. R.: Study of Acute Secondary Anemias in Infancy, Am. J. Dis. Child. **26**:291 (Oct.) 1923.

# THE CARBOHYDRATE METABOLISM OF THE NORMAL INFANT*

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In this paper, the results of our studies on some aspects of the carbohydrate metabolism of normal infants are presented. The infants were as nearly normal as it was possible to obtain in an active pediatric service.

## AVERAGE CONCENTRATION OF THE FASTING BLOOD SUGAR

Conflicting values have been reported for the average concentration of the blood sugar in fasting infants. A critical review of the literature shows that one reason for this at least, aside from inherent errors in the methods used or errors in the technic of the investigator, is that a number of the workers did not determine carefully the interval required after a meal for the blood sugar to return to the fasting level. It has been demonstrated by Niemann [1] and Rumpf [2] that, three hours after a feeding, the blood sugar concentration is frequently above the initial level, while from four to eight hours after a feeding it remains at practically a constant level. From our own studies we found a great variation in different infants, but in certain cases an interval of over three hours was required for the blood sugar to return to the original value.

Probably more studies have been made with the use of the Bang method than any other. Gotzky,[3] in 1913, found an average value for the fasting blood sugar of 0.095 per cent. during the first year. However, the blood was removed from the infant in many cases within an hour of the last feeding. If these values are omitted and only those considered in which the blood was removed four or more hours after the last feeding, the average concentration found is 0.077 per cent. Bing and Windelow [4] found an average value of 0.103 per cent., while Mogwitz [5] reported values which varied from 0.070 to 0.103 per cent. In

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* Read at the third annual meeting of the Canadian Society for the Study of Diseases of Children, Ottawa, Ont., June, 1925.
* From the Wards and Nutritional Research Laboratories of the Hospital for Sick Children and the Sub-Department of Pediatrics, University of Toronto.

1. Niemann, A.: Jahrb. f. Kinderh. **83**:1, 1916.
2. Rumpf, F.: Jahrb. f. Kinderh. **105**:321, 1924.
3. Gotzky: Ztschr. f. Kinderh. **9**:44, 1913.
4. Bing, H. J., and Windelow, O.: Ztschr. f. Kinderh. **9**:64, 1913.
5. Mogwitz: Monatschr. f. Kinderh. **12**:569, 1914.

neither instance did the authors wait four hours after the feeding before removing the blood. Niemann,[1] in 1916, found an average concentration of 0.077 per cent. Frank and Mehlhorn,[6] in 1920, obtained an average value of 0.086 per cent. in children about 2 years of age, while the very high figure of 0.123 per cent. was reported by Nysten [7] in 1921. Rumpf,[2] in 1924, found an average value of about 0.075 per cent. Taken on the whole, it is seen that the results obtained by the use of the Bang method are fairly constant, the values most frequently falling between 0.075 and 0.090 per cent.

Other results vary considerably. Cobliner,[8] who was the first to record blood sugar determinations on infants, found, by the use of the Bertrand method, an average value of 0.119 per cent. Bass,[9] with children aged from 2 to 14 years, obtained an average figure of 0.091 per cent. with the Lewis Benedict method. Using the same method, Salomon [10] found concentrations varying from 0.08 to 0.12 per cent. in children. An average value of 0.075 per cent. was found by Guy [11] in the blood removed from infants from three to four hours after the feedings. (Owing to a typographic error, the figure given in her paper is 0.068 per cent.) Using the McLean method, Spence [12] and Brown [13] obtained an average concentration in infants of 0.096 and 0.106 per cent. respectively.

The interesting observation has been made by Lucas and his co-workers,[14] Brown,[13] and others, that during the first two weeks of life the blood sugar is at a distinctly lower concentration than at any other period.

We determined the fasting blood sugar concentration in sixty-eight normal infants. These infants varied in age from 1 to 18 months. The blood was removed from the longitudinal sinus at least four hours after the previous feeding. The procedure used in the determination of the blood sugar is based on the Schaffer-Hartmann method and has been described elsewhere.[15] The results obtained were singularly constant. The average value found was 0.085 per cent. Of the sixty-eight cases,

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6. Frank, A., and Mehlhorn, L.: Jahrb. f. Kinderh. **91**:313, 1920.
7. Nysten, quoted by Brown, M. J.: Footnote 13.
8. Cobliner, S.: Ztschr. f. Kinderh. **1**:207, 1911.
9. Bass, M. H.: The Sugar Content of the Blood in Childhood, Am. J. Dis. Child. **9**:63 (Jan.) 1915.
10. Salomon, C.: Biochem. Ztschr. **90**:39, 1918.
11. Guy, R. A.: Quart. J. Med. **15**:9 (Oct.) 1921.
12. Spence, J. C.: Quart. J. Med. **14**:314 (July) 1921.
13. Brown, M. J.: Quart. J. Med. **18**:175 (Jan.) 1925.
14. Lucas, W. P.; Dearing, B. F.; Hoobler, H. R.; Cox, A.; Jones, M. R., and Smyth, F. S.: Blood Studies in the New-Born, Am. J. Dis. Child. **22**:525 (Dec.) 1921.
15. Tisdall, F. F.; Drake, T. G. H., and Brown, A.: J. Lab. & Clin. Med. **10**:704 (June) 1925.

in fifty-three the values found varied from 0.075 to 0.096 per cent. Only four were above 0.100 per cent., the highest value being 0.109 per cent., and only four were below 0.070 per cent., the lowest value being 0.058 per cent.

From a review of the literature and our own results, it would appear that the average fasting blood sugar concentration in normal infants usually does not vary more than from 0.075 to 0.095 per cent.

### THE EFFECT OF FEEDING VARIOUS SUGARS TO INFANTS ON THE CONCENTRATION OF THE BLOOD SUGAR

In 1903, Rohmann and Nagano [16] showed that of the three carbohydrates, saccharose (cane sugar), maltose and lactose, saccharose is absorbed from the gastro-intestinal tract most quickly, and lactose most slowly. These conclusions were based on experiments in which a measured amount of carbohydrate was placed in an intestinal loop of a dog for a stated interval, and then the amount of sugar remaining in the loop was determined.

Bergmark,[17] in 1914, determined the tolerance curves in infants after feeding saccharose, maltose and lactose, and his findings corroborate the conclusions of Rohmann and Nagano. The greatest increase in the concentration of blood sugar was obtained with saccharose and the least with lactose. Niemann [1] determined the blood sugar concentration after giving sugar with milk dilutions. He found tremendous differences in the response obtained with different normal infants. The highest values were usually reached in one-half to one hour after the feeding, but in some infants the blood sugar never increased above 0.100 per cent. while in others it reached the high concentration of 0.160 per cent. Frank and Mehlhorn [6] fed infants the very large quantity of 8 gm. per kilogram of body weight of cane sugar dissolved in tea. In from one-half to one hour the blood sugar usually reached the concentration of from 0.175 to 0.200 per cent. Owing to vomiting, similar observations with dextrose and lactose were not completed.

Other studies on the blood sugar concentration in infants after feeding have been reported by Gotzky,[3] Bing and Windelow,[4] Mogwitz,[5] Spence,[12] Rumpf [2] and Brown.[13] One of the most important conclusions to be drawn from these studies is that the sugar tolerance curve in infants is essentially the same as in adults after the oral administration of carbohydrate, except that the curve is much flatter. In other words, the sugar tolerance in infancy is greater than in adult life.

In the early part of our studies, we determined the effect on the blood sugar concentration of the oral administration of 1 ounce of the

16. Rohmann, F., and Nagano, J.: Arch. f. d. ges. Physiol. **95**:533, 1903.
17. Bergmark: Jahrb. f. Kinderh. **80**:373, 1914.

various carbohydrates in common use. We soon found that variable results were obtained in different infants with the administration of the same sugar. We then studied the effect of the oral administration of the different sugars to the same infant, but again no consistent results were obtained. As it was impossible to state whether these variations were due to differences in the rate of absorption from the gastro-intestinal tract, or to changes in the general carbohydrate metabolism, we decided to confine our investigation to a study of the effect of the parenteral administration of glucose.

### THE EFFECT ON THE CONCENTRATION OF THE BLOOD SUGAR OF THE SUBCUTANEOUS ADMINISTRATION OF GLUCOSE

Five, 10 and 15 per cent. solutions of glucose were injected subcutaneously into infants. The blood sugar was determined before the injection and at half hourly intervals after the injections for a period of three hours. The amount of solution given in each instance was 10 c.c. per pound of body weight. The time required for the injection was usually about fifteen minutes, although occasionally a longer period was necessary. In no instance were any local or general ill effects observed. From the clinical examination of the infant, no difference could be determined in the rate of absorption of the different solutions. The average values obtained are shown in Chart 1. The curves are plotted from 100 blood sugar determinations.

From a study of Chart 1, it is seen that the increase in the concentration of the blood sugar after the subcutaneous injection of 5 per cent. glucose is much less than that obtained with 10 and 15 per cent. solutions. However, there is no essential difference in the results obtained with the two latter solutions. The blood sugar concentration one-half hour after their injection is about 0.225 per cent., and it returns to its original level in from two to three hours. For the last two years 10 per cent. solutions of glucose have been used in this hospital in the routine subcutaneous administration of fluid. During this time as many as seventy-five injections a day have been made, with no local ill effects. Also, the clinical results obtained with the use of the 10 per cent. solution have been definitely superior to those obtained with the 5 per cent. solutions.

### THE EFFECT ON THE CONCENTRATION OF THE BLOOD SUGAR OF THE INTRAVENOUS ADMINISTRATION OF GLUCOSE

Ten cubic centimeters per pound of body weight of a 10 per cent. solution of glucose was injected intravenously into normal infants. The longitudinal sinus was used in every case. The time required for injection was usually less than five minutes. The average values obtained

from 163 blood sugar determinations are shown in Chart 2. It is seen that the concentration returns to the original level in from one to one and a half hours after the injection. It is thus evident that the injected glucose disappears from the blood stream with rather surprising rapidity.

The intravenous injection of 20 per cent. glucose with insulin has been recommended by Marriott.[18] In another communication [19] we have reported a study on the effect of the administration of insulin and glucose to infants. In Chart 2 is plotted a curve used in that study. This curve is obtained from forty-two blood sugar determinations in infants who were given 10 c.c. per pound of body weight of a 20 per cent. solution of glucose without insulin. It is seen that the concentration of the blood

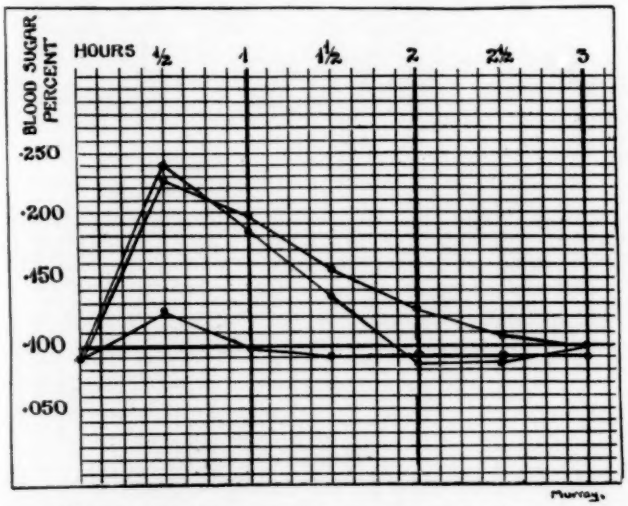


Chart 1.—The lower line represents the average sugar tolerance curve obtained after the subcutaneous administration of 10 c.c. per pound of body weight of a 5 per cent. solution of glucose to normal infants. The upper two lines represent the values obtained after the use of 10 and 15 per cent. solutions.

sugar is much greater than that obtained with the 10 per cent. glucose, and that from two to three hours are required for its return to the original level.

## COMMENT

The question arises as to what happens to the glucose after its parenteral administration to normal infants. We know it is removed from the blood stream with rather surprising rapidity. This rapid removal of glucose might be due to excretion by the kidneys, oxidation in the tissues or storage in the tissues.

18. Marriott, W. McK.: The Food Requirements of Malnourished Infants, J. A. M. A. **83**:600 (Aug. 23) 1924.

19. Tisdall, F. F.; Brown, A.; Drake, T. G. H., and Cody, M. G.: Insulin in the Treatment of Malnourished Infants, Am. J. Dis. Child. **30**:10 (July) 1925.

We determined the amount of glucose excreted by the kidneys after the intravenous administration of 10 c.c. per pound of body weight of a 10 per cent. solution of glucose. The infants were catheterized one and two hours after the injection and the bladder was washed out each time. The amount of glucose excreted during the second hour was found to be quite small. The total amount of glucose excreted was usually less than 2 per cent. of the amount injected. The highest value found was 5 per cent., and the lowest value was 0.7 per cent. It is quite evident

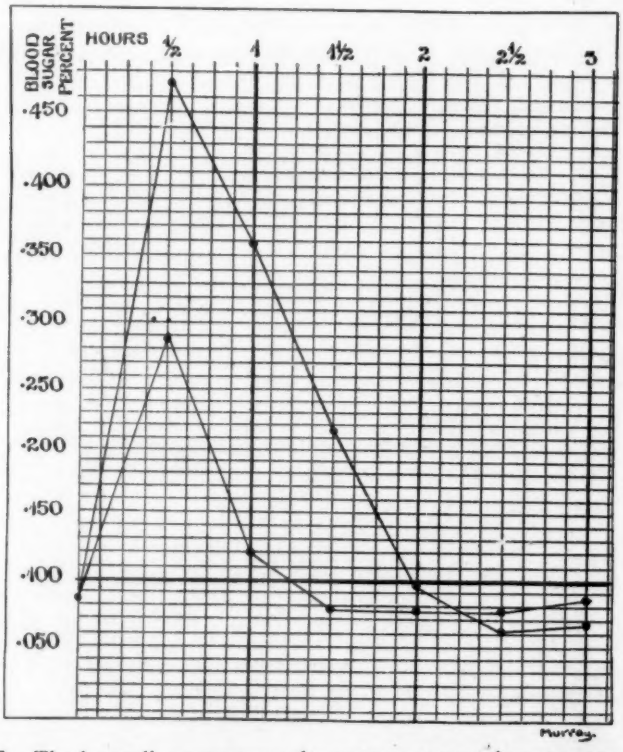


Chart 2.—The lower line represents the average sugar tolerance curve obtained after the intravenous administration of 10 c.c. per pound of body weight of a 10 per cent. solution of glucose to normal infants. The upper line is the average curve obtained after the administration of 20 per cent. glucose.

that excretion of glucose by the kidney does not account for the rapid removal of injected glucose from the blood stream of normal infants.

In regard to immediate oxidation or storage by the tissues, we have been unable to find any figures on infants. There are figures on the respiratory quotient but not before and after the injection of glucose. In adults, it is well known that there is a definite increase in the respiratory quotient after the ingestion of glucose, which indicates an increase in the

oxidation of carbohydrate. It has been calculated by Sanger and Hun [20] from their results on ten normal adults, that after the injection of 1.75 gm. of glucose per kilogram, only 18 per cent. of the ingested glucose was oxidized in the following two and a half hours. If we can apply these figures to infants, it would indicate that the greater part of the injected glucose is not immediately oxidized, but stored, either as glycogen or hexose-phosphate compounds [21] or changed to fat.

The question also arises as to what happens to the injected water. Is it excreted by the kidneys or stored in the tissues, or does it remain in the blood stream? In regard to the last question it has been shown by Magnus [22] that when large quantities of blood are injected into the blood stream from 30 to 55 per cent. of the injected fluid leaves the circulation within an hour. Even more striking are the results, reported by Bogert, Underhill and Mendel,[23] after the intravenous injection of physiologic sodium chlorid solution to rabbits. These investigators found that after the injection of an amount of physiologic sodium chlorid solution equal to the calculated blood volume, the original blood volume is restored in about thirty minutes.

We determined the concentration of the red blood corpuscles before, one-half hour and one and a half hours after the intravenous injection of 10 c.c. per pound of body weight of a 10 per cent. solution of glucose. The average concentration of the red blood corpuscles before injection in six infants was 5,527,000 per cubic millimeter, while one-half hour later it was 5,568,000 per cubic millimeter. One and one-half hours after the injection the count was 5,613,000. This indicates that the injected fluid was removed from the blood stream within half an hour of the time of its administration.

The injected fluid does not leave the blood stream immediately by way of the kidneys. The amount of fluid excretion during the two hours following the intravenous injection of 10 c.c. per pound of body weight was usually only about 10 per cent. of the amount administered, which indicates that there is no perceptible increase over the normal rate of excretion. This amount may even indicate a decrease in the normal rate of excretion. Bogert, Underhill and Mendel [23] found in their experimental work with rabbits that kidney activity was not essential for the regulation of the blood volume after the injection of fluid. They concluded that the tissues act as a reservoir for the injected fluid, and made the rather surprising observation that the tissues of the rabbit

20. Sanger, B. J., and Hun, E. G.: The Glucose Mobilization Rate in Hyperthyroidism, Arch. Int. Med. **30**:397 (Sept.) 1923.
21. MacLeod, J. J. R.: Canad. M. A. J. **15**:476 (May) 1925.
22. Magnus, Arch. f. exper. Path. u. Pharmakol. **45**:210, 1901.
23. Bogert, L. J.: Underhill, F. P., and Mendel, L. B.: Am. J. Physiol. **41**:189 (Aug.) 1916.

can store no less than four times the normal blood volume of the animal. We must also consider, as some of the injected glucose is probably stored as glycogen, that the glycogen molecule carries with it a number of molecules of water. We may conclude, therefore, that the injected fluid is removed from the blood stream with great rapidity and stored at least temporarily in the tissues.

## SUMMARY

From a review of the literature and our own results, it would appear that the average fasting blood sugar concentration in normal infants usually does not vary more than from 0.075 to 0.095 per cent. In the sixty-eight cases here reported, the average value found was 0.085 per cent.

The subcutaneous injection of 10 c.c. per pound of body weight of a 5 per cent. solution of glucose produced only a slight rise in the blood sugar concentration. The use of 10 and 15 per cent. solutions of glucose caused the blood sugar concentration to increase after an interval of one-half hour to about 0.225 per cent. The original level was again reached in from two to three hours.

The subcutaneous administration of a 10 per cent. solution of glucose has been carried out in several thousand cases with no local or general ill effect.

The intravenous administration of 10 c.c. per pound of body weight of a 10 per cent. solution of glucose caused an increase in the blood sugar level, which after an interval of one-half hour was at the average concentration of 0.290 per cent. The concentration of blood sugar decreased to the original fasting level in from one to one and a half hours after the injection. It is thus evident that the glucose was removed from the blood stream with rather surprising rapidity.

Only about 2 per cent. of the injected glucose was excreted by the kidneys.

The injected fluid was also removed rapidly from the blood stream. Very little, if any, of the fluid was excreted by the kidneys during the two hour interval following the administration. It would appear that the injected fluid was stored temporarily, at least, in the tissues.

# CRANIOTABES

## ITS PREVALENCE AND SIGNIFICANCE *

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AND
H. G. DENNIS, M.D.
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The earliest recorded description of craniotabes was made in 1843 by Elsässer,[1] who considered it a rachitic phenomenon. He defined this condition as areas of parchment-like bone found chiefly in the occipital and parietal regions. Friedleben,[2] in 1860, was the first to note its presence during the early weeks of life. Bohn [3] believed this early softening to be nonrachitic, but that appearing after the second or third month to be rachitic. Wieland,[4] after a study of 734 cases of craniotabes, most of which were found during the early months, concluded that none of the patients were rachitic, in spite of the fact that he found it more frequently in colored babies. He based his conclusions on the fact that the condition appeared when undisputed signs of rickets were few or absent and disappeared when other signs were progressing.

Among the more recent writers, Hess [5] believes that craniotabes appearing before the fifth or sixth month is not diagnostic of rickets, and regards this earlier softening as congenital osteoporosis. Huenekens [6] on the other hand, thinks it is the earliest sign of rickets and reports his findings in a group of rachitic twins and premature infants. DeBuys [7] also believes craniotabes to be a sign of rickets, and shows that from the second to the fifth month it is nearly twice as frequent among the colored as among the white children.

In our study, all degrees of abnormal cranial softening have been considered as craniotabes. Some areas were so small as to be palpable with the tip of the finger only, others so large as to involve a considerable portion of the top and back of the head. We have found that the bone

* Received for publication, July 15, 1925.

* Read before the North Pacific Pediatric Society, Seattle, Wash., Jan. 17, 1925.

1. Elsässer, C. L.: Der Weiche Hinterkopf, 1843.
2. Friedleben, A.: Jahrb. f. Kinderh. **3**, 1860.
3. Bohn: Jahrb. f. Kinderh. **22**, 1884.
4. Wieland: Virchows Arch. f. path. Anat. **95**, 1909.
5. Hess, A. F.: Abt's Pediatrics, Philadelphia, W. B. Saunders Company **2**, 1924.
6. Huenekens, E. J.: Rickets with Special Reference to Premature Infants, Journal-Lancet **37**:804 (Dec. 15) 1917.
7. DeBuys, L. R.: A Clinical Study of Rickets in Breast-Fed Infants, Am. J. Dis. Child. **27**:149 (Feb.) 1924.

around the mastoid fontanel and along the occipitomastoid suture [8] is usually the first to soften and the last to harden.

The observations included in this study were made on 193 white infants under 1 year of age, during the last half of 1923 and the first half of 1924. Some of these were seen in a clinic for well babies, and some in our private clinic. Of this group, 120, or 62.2 per cent., developed craniotabes at some time during their first year. This is a much higher percentage than is reported by most observers. In a group of breast-fed babies under 1 year of age, DeBuys [7] found craniotabes in 33⅓ per cent. of the white and 43.48 per cent. of the colored. Barenberg and Bloomberg [9] have recently reported finding it in 44.6 per cent. of patients under 1 year. The greater frequency of craniotabes in Portland is probably due to the greater prevalence of cloudy weather in the Pacific Northwest, the cloud center of the United States.

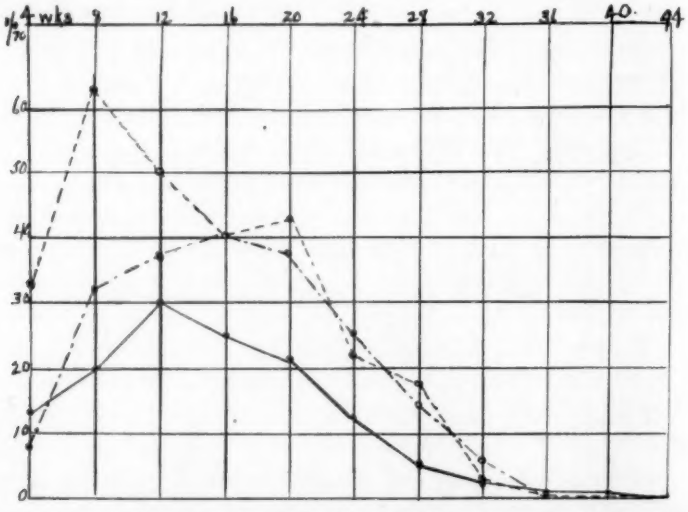


Fig. 1.—Age incidence of craniotabes. Solid line, one hundred twenty cases under one year; dotted line, twenty-eight patients first seen under two months of age and examined at least once a month throughout the year; dot and dash line, forty-three patients who had normal heads when first examined and who developed craniotabes when under examination.

Due to the infrequency of examination of some infants included in this report, we have arranged the data obtained into three groups:

First, the group as a whole.

Second, a group of forty-three babies who developed craniotabes while under observation.

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8. Moore, C. Ulysses: Newer Clinical Signs of Early Rickets, J. A. M. A. **83**:1469 (Nov. 8) 1924.

9. Barenberg, L. H., and Bloomberg, M. W.: The Significance of Craniotabes and Bowing of the Legs, Am. J. Dis. Child. **28**:716 (Dec.) 1924.

Third, a group of twenty-eight, first seen under 2 months of age, and examined biweekly throughout the year.

### TIME OF APPEARANCE

In the entire group of 120 cases, craniotabes was most frequently observed for the first time at the third month. To ascertain how early this symptom appeared, a separate study was made of a group of twenty-eight infants who came under observation before the age of 1 month. These babies nearly all developed flexibility of the cranial bones during the first 2 months of life. Very few of them developed craniotabes after the fifth month. All of these twenty-eight infants later developed undisputed signs of rickets, such as rosary, groove, epiphyseal thickening, bow-legs or knock-knees. In most cases, several of these abnormalities

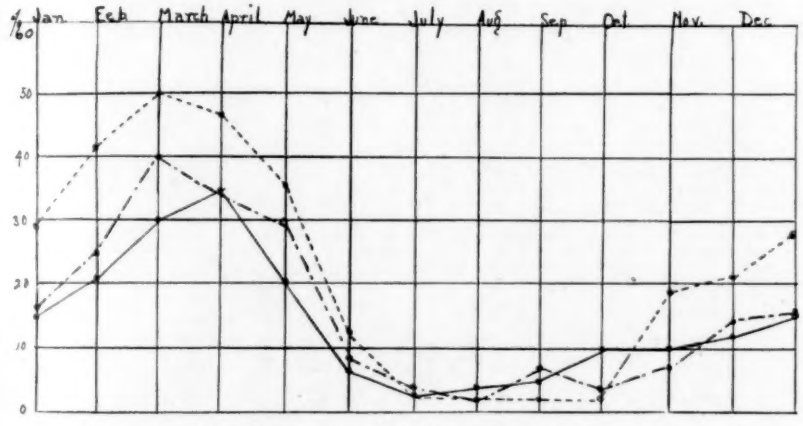


Fig. 2.—Seasonal incidence of craniotabes. Symbols mean the same as in Figure 1.

were found. The onset in the group of forty-three (who developed craniotabes while under observation) was within the same age limits as that of the preceding group.

In each of the groups the incidence of cranial softening (Fig. 1) was greatest between the second and fifth months. It was found very infrequently after the seventh month and practically not at all after the eighth. In every case as soon as the condition was noted, cod liver oil was given either to the mother or to the babe. In addition, whenever possible, treatments with ultraviolet irradiation were instituted.

It has long been recognized that all signs of active rickets are more prevalent during the spring months than at any other time of the year. Likewise in all three of our groups the greatest number of cases of craniotabes was found in March and April. A rapid decrease was noted

in the month of May, 1924 (an unusually sunny month), followed by an almost total absence of the symptom during the summer (Fig. 2). The number of cases of craniotabes began to increase appreciably in November, a few weeks after the beginning of cloudy weather in this climate.

The frequency and severity of rickets are greater in the spring. This is also true with craniotabes as shown in Figure 3, which represents fifty-two patients who were examined regularly throughout the course of the craniotabes. The maximum severity was reached during March and April, and in only a few cases was there marked flexibility during the summer months.

## CASE HISTORIES

CASE 1.—*History.*—H., a girl, breast-fed, was born Jan. 1, 1924, and was examined for the first time when 22 days of age. The head was normal and the other physical findings were negative for four successive examinations. On the fifth examination, at the age of 6 weeks, craniotabes was noted for the first time.

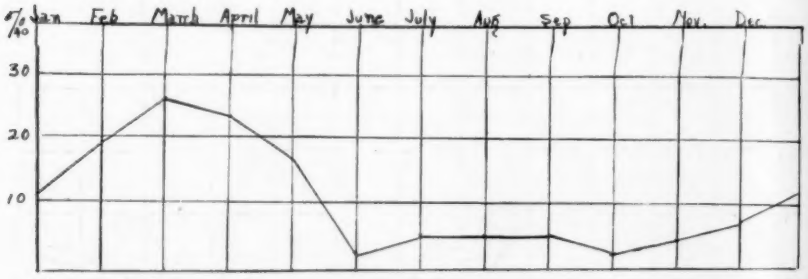


Fig. 3.—Incidence of greatest severity in craniotabes, in fifty-two patients followed throughout the period of flexibility.

The area of flexibility was as indicated in Figure 4. The only treatment given consisted of 1 teaspoon of cod liver oil three times a day to the mother. The craniotabes remained unchanged until the baby was 5½ months old, when one-half teaspoon doses of cod liver oil three times a day were given to the baby herself and heliotherapy was begun. One month later the extent of softening was appreciably smaller. During this time such defects as a slight rosary and moderate costal flaring had developed. We did not see the baby again until October 14, when she was 9 months old. At this time the craniotabes had entirely disappeared but a slight rosary and a definite epiphyseal enlargement were present.

CASE 2.—*History.*—C., a boy, whose twin died at birth, was examined for the first time Sept. 22, 1923, when he was 13 days of age. At that time and at the next three examinations there was no cranial softening. When 2 months old (Fig. 5), an interval of one month having elapsed since the previous examination, he was found to have moderate craniotabes, a quadratic head and a very flat chest. These abnormalities had developed in spite of the fact that since 5 weeks of age, the baby had been taking 10 drops of cod liver oil three times a day. This had been prescribed because an older sister and the mother had had rather severe rickets. At 2 months of age, the cod liver oil was increased to one-half teaspoonful three times a day and treatments twice a week with the mercury quartz lamp were commenced. At 4 months of age, the cranial softening was

much improved, but the head was still square and the bosses were very prominent. A rosary and a definite Harrison's groove had developed, and there was a moderate degree of epiphyseal enlargement at the wrists. The craniotabes gradually improved and entirely disappeared during June at the age of 9½ months. At this time the head remained square with posterior flattening, the chest a flattened oval at the xiphoid plane with a marked rosary and groove, and the abdomen distended; there was also a rachitic curvature of the vertebral column. At 13 months of age, all these evidences of rickets had considerably improved.

## COMMENT

The purpose of this study is to draw attention to the prevalence of craniotabes in this section of the country, and to determine its significance if possible.

Fig. 4.—H., aged one month. The parts of the cranium included within the dark lines show abnormal flexibility.

During the first 6 months of life the skull makes its most rapid growth, the increase in capacity being 75 per cent. At this time the cranium is growing more rapidly than any other part of the body and the occipital portion faster than the parietal or frontal portions. It is at this age and in this part of the skull that craniotabes is most frequent, just as later the rosary and the epiphyseal enlargements appear at the time of most rapid growth of the bones involved, and in that part of the bone in which the greatest development is taking place.

The seasonal incidence of craniotabes is the same as that of undisputed signs of rickets, being greatest during the spring months and almost nil during the summer season. Not only is it most frequent but it is also most severe during March and April.

Wieland [4] and DeBuys [7] have shown that this disorder, like undisputed rachitic symptoms, is much more prevalent among colored than among white children.

Irrespective of the age at which the cranial softening appeared or whether or not it developed during the period of observation, the duration, the age of its greatest frequency, seasonal incidence and the period of greatest severity were practically the same.

Rachitic abnormalities such as rosary, groove, thickened epiphyses, and bow-legs or knock-knees, appeared much more frequently in these babies than in those who did not develop craniotabes.

Fig. 5.—C., aged three and one-half months. Craniotabes and prominent bosses were noted at two months of age.

Craniotabes responds to the same therapy as rickets. It improves slowly under cod liver oil and rapidly under ultraviolet light or exposure to the direct rays of the sun.

## CONCLUSIONS

In the study of 193 infants under 1 year of age, cranial softening was found in 62 per cent. Our cases indicate that craniotabes is rachitic because:

1. It develops in the most rapidly growing portions of the skeleton, the head, during the first 6 months of life. When this rapidity of cranial growth diminishes and craniotabes is consequently disappearing, abnormal bone growth may begin in some other rapidly developing portion of the skeleton. Thus craniotabes may be improving when costomalacia is increasing or the epiphyses are enlarging.

2. It appears in that portion of the skull which is growing most rapidly. We have found that the area first to soften and last to harden is in that part of the occipital bone adjoining the mastoid fontanel.

3. It is found more frequently in colored children, as are other forms of rickets.

4. It is more prevalent in the Pacific Northwest than in sections of the country having more sunshine.

5. It occurs most frequently during the months of March and April.

6. It is most severe in the spring months.

7. The reactions of the entire group were similar to those patients with craniotabes generally admitted to be rachitic.

8. It is cured by antirachitic treatment.

9. It is frequently followed by undisputed signs of rickets in other parts of the body. When craniotabes is demonstrated, one may anticipate finding a concurrent or later development of costomalacia, rosary, Harrison's groove, pot belly, enlarged epiphyses, flat-feet and knock-knees or bow-legs.

914 Corbett Building.

# GUMMATOUS OSTEOPERIOSTITIS OF THE SKULL IN CONGENITAL SYPHILIS

## REPORT OF TWO CASES *

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NEW HAVEN, CONN.

In a series of 100 cases of congenital syphilis in the University Clinic during a period of three and a half years, two children have presented themselves with gummatous osteoperiostitis of the skull, in addition to other lesions of congenital syphilis. The interest in these cases lies in the rarity of involvement of the skull in the gummatous process, and in the scarcity of reports of this condition.

### CASE REPORTS

CASE 1.—H. Z., a girl, Polish, aged 8 years, was admitted to the New Haven Hospital, Feb. 17, 1919, with the complaint of "sores on the legs."

*Family History.*—The patient's father died at the age of 37, following an operation on the jaw. He was said to have been tuberculous. The mother is living and well. There are two sisters and three brothers living and well. One child died at 2 weeks and one at 6 months of age. The patient was the sixth child.

*Past History.*—The patient was very small at birth; the exact weight is not known. She was breast fed for eleven months. When 1 month old, lesions developed on both frontal eminences of the skull. These broke down and discharged and healed spontaneously. She had measles at 3 years of age; at this age she "went blind" and was treated in the New Haven Dispensary for interstitial keratitis. Later, another "sore" developed on the forehead and at 5 years of age "sores" appeared on the shins and persisted until the time of admission.

*Physical Examination.*—This was performed by Dr. J. I. Linde. The head showed a depression (4 by 1 cm.) in the median line of the upper part of the forehead, covered by a smooth white scar. There was external strabismus of the right eye and a corneal scar. The pupils were somewhat dilated. A nasal discharge was present and all of the lymph glands were enlarged except the epitrochlears. The upper middle incisors were notched, pegged and carious. The spleen was not enlarged. A smooth, white, adherent scar on the right leg extended from the knee to the ankle. There was an ulcer on the left leg and the left knee was somewhat swollen. The Wassermann test of the blood was 4 plus in both antigens. The roentgen-ray examination showed marked changes in the skull and long bones. Both fibulae showed periostitis and osteitis as did the skull.

The patient received inunctions of diluted mercurial ointment, seven doses of an arsenical intravenously, and was discharged April 19, after two months in the hospital. The discharge note stated that the ulcer on the left leg was smaller and that dead bone was present at the base of the ulcerated area. The Wassermann reaction was still 4 plus. In June, 1921, she was seen in the eye clinic in the New Haven Dispensary and there were maculae on both corneas and posterior synechiae of the right iris. In September, a divergent squint of the right eye was noted. The patient was seen by me in the pediatric clinic on October 14. The examination at that time showed a large white scar in the middle of forehead;

* Received for publication, July 7, 1925.

* From the Department of Pediatrics, Yale University School of Medicine and the Pediatric Service of the New Haven Hospital and Dispensary.

external strabismus of the right eye; the right pupil smaller than the left and irregular; the upper middle incisors notched and pegged, and scars on anterior surfaces of both tibias (Figs. 1 and 2).

The Wassermann test was repeated and found to be 4 plus in both antigens. Neither the patient nor her mother would cooperate, with the result that only a few treatments have been given at very irregular intervals.

CASE 2.—P. G., a girl, Italian, aged 8 years, was admitted to the New Haven Hospital, April 25, 1924, with a complaint of "sores on the forehead, arms and legs."

Fig. 1 (Case 1).—Smooth white scar on forehead, external strabismus of right eye and Hutchinson's teeth.

*Family History.*—The father admitted having had a sore on the genitalia. The mother had had some sort of growths on the vulvae. The first pregnancy resulted in a miscarriage at seven months. There are two brothers and one sister living and well. One child died at the age of 2 years. The patient was the result of the third pregnancy.

*Past History.*—The patient was born at full term and is said to have weighed 10 pounds. Her development was normal. She gave a history of pneumonia, bronchitis, measles and empyema. Three years previous to admission she had a

bilateral conjunctivitis which lasted about two months. Shortly afterward, she developed a discharge from both ears which also lasted for about two months and resulted in deafness.

*Present Illness.*—About two and a half years ago, reddish blue lumps appeared on the patient's forehead, which broke down and discharged. The same kind of swelling then appeared on the left elbow and the left leg. These lesions healed

Fig. 2 (Case 1).—Scars on both shins and deformity of right leg.

and then recurred in about two months in new sites. The patient had some treatment with mercury. One month ago, the "sores" appeared on the forehead and legs and on this account she entered the hospital.

*Physical Examination.*—The patient was an undernourished and underdeveloped girl, pale, and appearing older than her age would indicate (Fig. 3). The following points were noted: Both pupils were irregular, the left pupil was small; both pupils reacted sluggishly to light; there was some cloudiness of the right cornea and a small scar on the right pupil. The patient was deaf. The teeth

were carious and irregular, the upper middle incisors being absent. There was loss of power of complete extension in both elbow joints; the knee joints were enlarged. There was an ulcer on each frontal eminence covered with a yellowish discharge, a similar ulcer being present on the left elbow with a sinus at the base extending into the bone. On the anterior surface of the left tibia was a red fluctuant mass about midway between the ankle and the knee which seemed to be continuous with the bone. The right ankle was involved in a similar

Fig. 3 (Case 2).—Multiple lesions involving head, arms and legs.

manner. On the inner surface of the left ankle was a white, depressed circular scar. Tests for hearing demonstrated slight, if any, tone perception in the right ear, none in the left, and no vestibular response from the caloric test. An examination of the eyes showed slight opacity of the lateral margin of the iris of the right eye and slight steaming of the cornea. There was irregularity of the left pupil, the condition being interstitial keratitis.

*Laboratory Findings.*—Red blood cells, 4,312,000; white blood cells, 6,900; polymorphonuclears, 73 per cent.; lymphocytes, 25 per cent.; hemoglobin, 50

per cent. The urinalysis was negative. The Schick test was positive. The Wassermann reaction of the blood was 4 plus in both antigens. Lumbar puncture fluid showed 9 cells, a negative globulin and Wassermann reaction, and colloidal gold, 2233100000. The roentgenogram of the bones of the skull and extremities showed syphilitic osteomyelitis.

*Treatment.*—The patient was given 8 doses of sulpharsphenamin subcutaneously at weekly intervals, a total of 2.64 gm. The skin lesions were covered with sterile dressings and boric acid ointment was applied around the edges of the ulcers to prevent the dressings from adhering to the wound, but no local treatment was used. Figure 4 shows the appearance of the lesions on the forehead before and after three weeks of treatment. Figure 5 shows the appearance at the end of the fifth week and at the time of writing. A decrease in the size of the lesions took place at the end of the first week; the discharge disappeared and scabbing took place at the end of the second week; healing was practically complete at the end of the third week. The gummas on the legs healed somewhat more

Fig. 4.—*a*, gummas of forehead before treatment; *b*, gummas of forehead after three weeks of treatment.

slowly. In the eight weeks' stay in the hospital the patient gained 1.1 kg. The lesions on the forehead healed completely except for a slight scab formation. A small sinus was still discharging from the left tibia and there was a small area of denuded dead bone on the left elbow. The sequestrum was discharged from the left elbow in three and a half months and that from the left tibia in four months. Complete healing took place without surgical intervention. The elbows, which could not be extended completely, regained almost perfect function, but the so-called "knock-knee elbow" deformity described by Stoll[1] remained. Figure 6 is a roentgenogram of the skull on admission. Figure 7 is a roentgenogram of the left ulna taken at monthly intervals. They show the gradual discharge of the sequestrum from the ulna; complete healing of the sinus and the skin followed. The same sequence of events occurred in the case of the sinus on the leg. No local treatment or surgical intervention was found necessary.

1. Stoll, H. F.: The Clinical Diagnosis of Heredosyphilis, J. A. M. A. **77:** 921 (Sept. 17) 1921.

## REVIEW OF LITERATURE

Numerous changes in the skull are described in congenital syphilis, but the type referred to as gummatous osteoperiostitis, if one may judge by the scarcity of references to it, is rarer in the congenital than in the acquired form of this disease. There is no doubt that changes in the skull due to rickets have frequently been confused with those due to syphilis.

Gummas may occur as early or late manifestations. They may involve the outer or inner table of the skull (Wegener),[2] or the dura itself (Ashby and Wright),[3] or the dura and brain (Adson).[4] Moro [5]

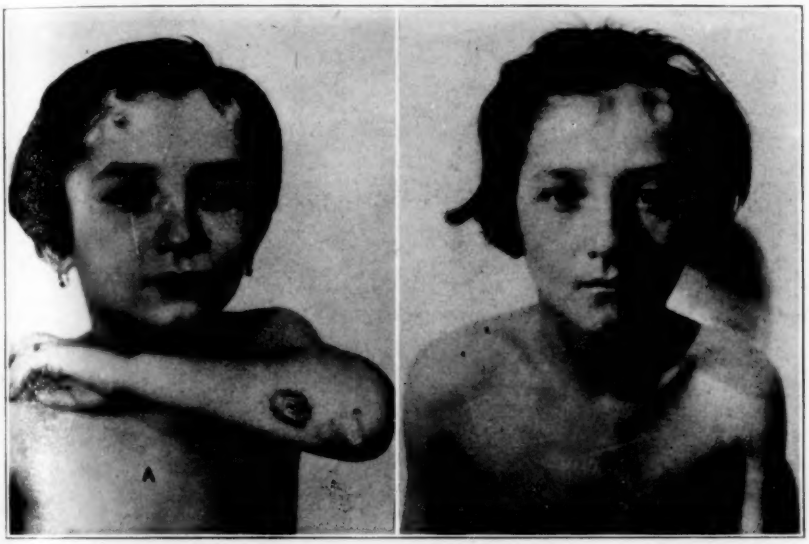

Fig. 5.—Appearance of lesions after five weeks of treatment, *a*, and appearance at time of writing, *b*.

and Zappert [6] give illustrations showing gummas of the frontal bones in children with congenital syphilis, but there is no discussion of the lesions in the text. Veeder and Jeans [7] also give an illustration of a

2. Wegener: Quoted by Pommer, footnote 10.

3. Ashby, H., and Wright, G. A.: The Diseases of Children, London, 1922, p. 705.

4. Adson, A. W.: Surgical Treatment of Gummatous Osteitis of the Skull, J. A. M. A. **74**:385 (Feb. 7) 1920.

5. Moro, E.: Text-Book of Pediatrics, Edited by E. Feer, Philadelphia, J. B. Lippincott Co., 1922, p. 769.

6. Zappert, J.: Pfaundler and Schlossman, Handbuch der Kinderheilkunde, Ed. 3, Leipzig, F. C. W. Vogel, **2**:528, 1923.

7. Veeder, B. S., and Jeans, P. C.: Abt's Pediatrics, **5**:635, 1924, Philadelphia, W. B. Saunders Company.

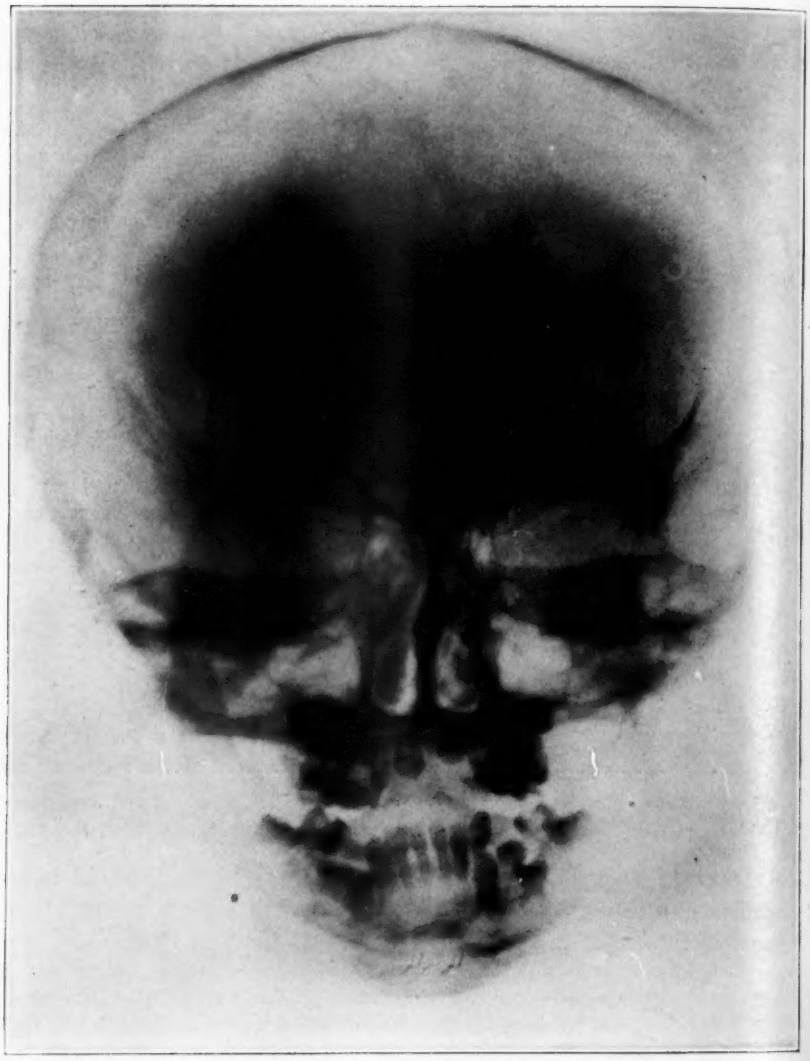

Fig. 6.—Roentgenogram of skull on admission.

congenitally syphilitic child with a gumma of the frontal bone, and state that not infrequently gummatous changes are seen which frequently degenerate and produce sinus formation.

Only one case report has been found in the recent literature (since 1916), namely, that of Ambrus.[8] He described an infant, aged 11 months, who entered the clinic with alimentary intoxication. The history stated that the baby was born at full term and was breast fed for nine months. For four months the parents had observed abscesses appear on different parts of the body. The father and mother were said to be

Fig. 7.—*a*, gumma of left ulna, appearance on admission; *b*, same after three weeks of treatment; *c*, the sequestrum being discharged into the soft parts; *d*, the sequestrum has been discharged and healing is complete.

well. The physical examination of the child showed symmetrically placed swellings on both frontal eminences, one the size of a walnut, and one somewhat smaller. The skin over them was intact and around the periphery of both could be felt bony rings. The orbit was involved on the left side. There was a swelling in the triceps muscle on the right. the elbows were affected so that extension of the right elbow was limited to 130 degrees. There was a discharging sinus in the fourth

8. Ambrus, J.: Ueber Gummöse Syphilis in Säuglingsalter, Jahrb. f. Kinderh. **101**:231-235 (March) 1923.

metacarpal bone. Both shins were thickened. The swellings on the forehead and on both elbows were diagnosed as gummatous syphilis. The blood Wassermann test was 3 plus. The patient died of pneumonia, and the diagnosis of syphilis was confirmed at necropsy.

No discussion of the treatment of gummatous osteitis of the skull has been found, so far as local treatment is concerned. Systemic treatment for syphilis is, of course, advocated. In 1920, Adson [4] reported on the surgical treatment and stated that "the ulcers do not respond to specific treatment or local application unless the sequestrum has been removed. The necrotic areas may persist for years until sufficient necrosis takes place to loosen the sequestrum, when granulation follows."

The pathologic reports of gummatous osteoperiostitis of the skull are more numerous than the clinical reports. The pathology of this lesion in congenital syphilis differs in no way from that in the acquired form. This is fully and ably described by Schmidt [9] as well as others, and need not be given in detail here. Interesting discussions of the gummatous changes in the skull in congenital syphilis are given by Pommer [10] and Wieland.[11]

### DIAGNOSIS

Gummas involving the skull are so regularly associated with other signs of congenital syphilis that the diagnosis presents little difficulty. As Schüller [12] points out: ". . . When osteoperiostitis progresses to the point at which the bone softens and the soft tissues are involved and gumma formation takes place, the differentiation from rickets is no longer necessary." Tuberculous osteomyelitis may involve the skull. While syphilis attacks the frontal and parietal bones most commonly, tuberculosis usually attacks the temporal and malar bones. The roentgen ray, moreover, besides showing the defects in the skull with "sharp, crescentic or kidney-shaped edges," characteristic of syphilis, may reveal syphilitic changes in other bones (periostitis or osteomyelitis). It is the rule in syphilis to have lesions in more than one bone, while in tuberculosis the opposite finding is common. Wieland, writing from the point of view of the pathologist, lays stress on the worm-eaten appearance of the sequestrum in syphilis and the presence of a process of new bone formation in the neighborhood of the syphilitic

9. Schmidt, M. B.: Pathologie des Knochensystems. XIX. Die Knochensyphilis. Ergebn. der Allgem. Path. **7**:254-255, 1900-1901.

10. Pommer: Zur Kenntnis der Hereditären Shädels-syphilis Vorhandlungen der deutschen path. Gesellschaft. **9**:312, 1905.

11. Wieland, E.: Die Kongenitale Spätsyphilis des Skeletts, Handb. d. path. d. Kindes. **2**:238-239, 1913.

12. Schüller, A.: Roentgen Diagnosis of Diseases of the Head, English Translation by F. F. Stocking, St. Louis, C. V. Mosby Co., 1918.

necrosis. Lovett and Wolbach [13] discuss the difficulty in diagnosing tuberculosis, osteomyelitis and syphilis by means of physical and roentgen ray examination. They stress the prevalence of the destructive type of lesion in tuberculosis, rapid destruction with marked formative activity in pyogenic osteomyelitis and a more purely formative type of process in syphilis. Tumors of the skull are rare in children, but myeloma, sarcoma, hypernephroma and neuroblastoma may metastasize to the skull. Here again the presence of signs of syphilis other than the lesions in the skull and a positive Wassermann reaction, with characteristic changes in the bones demonstrable by the roentgen ray, make the diagnosis of syphilis clear.

## SUMMARY

Two children have been seen with gummas of the skull in this clinic. The bones and skin were involved without evidence of involvement of the brain or meninges. The lesions healed rapidly under general antisyphilitic treatment. In spite of the formation of sequestrums, surgical treatment was not necessary to bring about complete healing, as evidenced locally and in the roentgen ray. Healing of the bones took place more slowly than healing of skin lesions, but was finally complete. While gummas of the skull occurred in the cases reported as a manifestation of late congenital syphilis, they may occur early, as in the case reported by Ambrus.

13. Lovett, R. W., and Wolbach, S. B.: Roentgenographic Appearance, Diagnosis and Pathology of Some Obscure Cases of Bone Lesions, Surg., Gynec. & Obst. **31**:111-131 (Aug.) 1920.

# PROGRESS IN PEDIATRICS

## REVIEW OF THE LITERATURE ON INFANT FEEDING FOR 1924 *

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### BREAST FEEDING

Richardson [1] has proved by statistics that the breast-fed baby has five times the chance for life and health as the artificially fed infant. He believes that every mother, when given intelligent instruction, can nurse her baby indefinitely, providing the breasts are emptied regularly at alternate feedings. The best means of stimulating secretion is by nursing or by rhythmic expression of the milk by the thumb and forefinger, applied just back of the nipple. This procedure should immediately follow the cessation of the nursing. Another method is the use of the breast pump. He finds that laboratory examinations of breast milk are useless unless a twenty-four hour specimen is taken. The so called colic in breast-fed infants is often a hunger symptom, which may be verified by putting the child back on the breast. Eructations of gas during the nursing are caused by air which has filled the stomach previous to the milk. Vomiting may be caused by the automatic return of excess milk, by an air bubble, or by some external physical factor, such as a tight band or sudden jolting.

Among the numerous causes for disappearance of breast milk are sudden grief, shock, reappearance of menstruation, severe diarrhea, or physical exhaustion with loss of sleep and weight.

Chapin [2] believes that the greatest effort for breast feeding should be made during the first month of life. Important factors in lessening infant mortality are prenatal supervision, natal care, more breast feeding, baby health stations, improvement in the production of cow's milk, and visiting nurses. The artificially fed infant more frequently develops signs of malnutrition than the breast fed, even if the secretion is poor. Chapin places the infant on both breasts at regular feeding time, followed by manual expression of the remaining milk. He urges the establishment of stations for the distribution of breast milk at maternity hospitals or community health centers.

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* Received for publication, Oct. 3, 1925.

1. Richardson, F. H.: The Technic of Breast Feeding, Arch. Pediat. **41**: 89 (Feb.) 1924.

2. Chapin, H. D.: The Management of Undernourished Infants, J. Missouri M. A. **21**:37 (Feb.) 1924.

In a study of 663 infants, Botts [3] has considered the types of feeding employed, and the physical side of children lacking medical care and supervision. One of the outstanding faults was the low incidence of breast feeding; 71 per cent. were nursed for only one week. The general physical condition of artificially fed infants was less encouraging than that of breast fed infants. A detailed chart shows the difference by comparison of muscle tone, nutrition, rickets and other defects. One half of the artificially fed children received pasteurized milk.

Chisholm [4] and McKay,[5] in a complete analysis on the subject of breast feeding, advocate the early changing of the feeding time from three to four hours. They also consider weak, overfed and underfed babies. For the very weak baby who is unable to nurse, the milk is drawn off and fed with a Breck feeder or a spoon. For the delicate child, who has difficulty in digesting full human milk, they suggest diluting it one-half. When mother's milk is not available, they believe breast milk should be obtained from a foster mother who can easily give three feedings each day.

Erdhuetter,[6] in discussing the hazard figures in infants fed by wet nurses, reports on 461 children, with an average entrance age of 26 days and an average exit age of 130 days. A hazard figure of 1.8 per cent. was found in 47,371 days of life. Among the common diseases transmitted by the wet nurse to the nursling were bronchitis, bronchopneumonia, and cystitis. He also found three cases of tuberculosis, of which one was fatal.

Reber [7] regards sterilized breast milk as a valuable food in the campaign against infant mortality, although he has found that fresh breast milk is decidedly superior to sterilized breast milk.

Varrier-Jones [8] has investigated the cellular content of milk, with the object of detecting the presence of pus. The only method of differentiating pus cells from normal leukocytes is by staining and by differential count. The usual method of investigation is to take three samples of milk (fore milk, middle milk and stripping). These different specimens are examined on glass slides, after being stained

3. Botts, E. L.: Unsupervised Diets of Infants up to One Year of Age, California & West. Med. **22**:485 (Oct.) 1924.

4. Chisholm, C.: Breast Milk Feeding, Lancet **1**:425 (March 1) 1924.

5. McKay, F. L.: Infant Mortality in Relation to Breast Feeding, New York State J. M. **24**:433 (March 28) 1924.

6. Erdhuetter: The Hazard Figure in Infants Fed by Wet Nurses, Ztschr. f. Kinderh. **36**:206, 1923.

7. Reber, M.: Sterilized Breast Milk as Food for Infants, Schweiz. med. Wchnschr. **54**:198 (Feb. 21) 1924.

8. Varrier-Jones, P. C.: The Cellular Content of Milk. Variations Met with Under Physiologic and Pathologic Conditions, Lancet **2**:537 (Sept. 13) 1924.

with Jenner's stain and dried. A high cell count does not necessarily suggest a disease of the udder, as normal cows of different breeds have different cell proportions in the milk. The fore milk usually contains lymphocytes and polymorphonuclear cells, in addition to colostrum corpuscles. As the milk becomes normal these decrease in number, but in the presence of an inflamed udder the polymorphonuclear variety increases. An acute infection of the udder forms true pus with a fall in the fat content of the milk. Abscess formation involving the glands is associated with a large number of polymorphonuclear cells. From observations, the cells in the milk are partly blood cells, lymphoid cells and epithelium.

Funkhouser [9] considers it more rational to use every available method of modifying breast milk to the digestive tolerance and the capacity of the infant, rather than to wean it prematurely. One of the important steps in solving the problem of breast feeding is regular weighing of the child before, during and after the nursing; this indicates whether the child is getting enough milk. If the intake is beyond the capacity, the feeding time may be shortened and only one breast given; if, however, the quantity received at a nursing is not sufficient, both breasts should be emptied each time. Complementary feeding is often resorted to as a temporary measure, but completely draining the breasts at regular intervals usually stimulates the glands and increases the output. When the fat content is abnormally high, there is vomiting shortly after the feeding with the appearance of fat curds in the stools. This condition may be corrected if the mother takes sufficient of a well balanced diet. He has found that neurotic mothers often disturb their milk to such an extent that their babies suffer from indigestion. A careful study and correction of the mother's habits and environment will produce excellent results.

In considering the modification of breast milk, Donnelly [10] agrees that laboratory tests are not reliable guides for weaning. In many cases, he finds it preferable to modify the breast milk, either before or after ingestion, by complementary feedings. Breast milk may be increased by giving both breasts at each nursing, by increasing the intake of fluids, by proper exercise and by adequate rest. The solids are increasing by shortening, and decreased by lengthening, the interval between feedings. The vitamin content depends on the mother's diet. Digestive disturbances are sometimes due to sensitization to certain proteins transmitted by the mother's milk. Complementary feedings may be given with low sugar content, such as buttermilk or albumin milk, using saccharin instead of sugar.

9. Funkhouser, W. L.: Modified Breast Milk, J. M. A. Georgia **13**:290 (July) 1924.

10. Donnelly, W. H.: Modification of Breast Milk, New York State J. Med. **24**:255 (Feb. 29) 1924.

Koeppe [11] agrees with many authors that the qualitative analysis of milk is valueless. He does not uphold the idea that breast milk is always good and that quantity determinations are sufficient, but attributes the disturbances in breast-fed infants to high or low fat content. By laboratory tests he has found that a constant proportion exists between the cream layer and the fat. This has been developed into a simple formula, by which the amount of fat present may easily be determined. The same formula is employed for calculating the energy quotient, thereby confirming Heubner's statement that an energy quotient of over 100 is necessary for the breast-fed child to thrive.

Hofmann [12] also uses the cream method in calculating the fat content of breast milk, as it has the following advantages: (1) it requires little milk, (2) it is cheap, and (3) it may be carried out anywhere. During a feeding, five samples are expressed from the breast. The amount of milk taken by the child is measured by weighing before and after the feeding, so that the percentage of fat content may be accurately estimated. Analysis has shown that individual feedings may vary greatly in the percentage of fat content, but these variations are compensated for during twenty-four hours; the first feeding is always largest. Contrary to Koeppe,[11] Hofmann [12] considers a single analysis during the day sufficient.

In some recent work by Smith and Emerson [13] on dried breast milk, in which they used the Just-Hatmaker process, the average composition of the milk was found to contain 30 per cent. of fat, 60 per cent. of carbohydrate and 10 per cent. of protein. The composition of the milk was fairly uniform even when obtained from different women. It is hoped by this experiment to establish centers where mothers, after proper physical examination, may have their breasts emptied and the milk dried for clinical use.

Canelli [14] has observed the influence of menstruation on lactation in 715 nursing women. The first menstruation usually appears four and a half months after the child's birth. Fifty-two per cent. of the cases observed occurred between the second and fourth month. In 90 per cent. of the cases the menstrual period was identical in duration with that before pregnancy. In 30 per cent. of the infants the weight diminished during the menstrual period. In 17 per cent. nursed during men-

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11. Koeppe, H.: The Clinical Value of Fat Determination in Breast Milk, Jahrb. f. Kinderh. **106**:177 (July) 1924.

12. Hofmann, A.: Fat Determination in the Amount of Breast Milk Imbibed Daily by an Infant, Jahrb. f. Kinderh. **106**:310 (Aug.) 1924.

13. Smith, L. W., and Emerson, P. W.: Notes on the Experimental Production of Dried Breast Milk, Boston M. & S. J. **191**:838 (Nov. 13) 1924.

14. Canelli, A. F.: Menstruation and Lactation, Nourrison **12**:92 (March) 1924.

struation there was diarrhea at the time or shortly after, but the loss of weight and the infantile diarrhea were of short duration and did not affect the child's health or growth.

### BOTTLE FEEDING

Fry [15] has attempted to assemble the fixed principles of infant feeding. He makes the plea for the formulation of some broad process, acceptable to all and practical enough to serve as a guide in prescribing food. This would give medical students a reasonable amount of uniform teaching, based on research and confirmed by definite well established clinical observations. It would at the same time prevent any free speculation or experiment. The following general plans are suggested as suitable to meet these requirements: (1) there is no artificial food suitable to all infants; (2) feeding must be in part empirical, as infants often have a reserve digestion and may thrive well on different foods; (3) human milk is still the best food; (4) in normal cases, artificial food, which most resembles human milk should be preferred; (5) calorific feeding is the most accurate means of measuring the food requirement; (6) protein milk is a temporary therapeutic agent with only very definite indication; (7) maltose is absorbed in larger proportion than other sugars and often produces a striking gain in weight. However, it is less laxative than other sugars, because it is absorbed higher up in the alimentary canal.

Finkelstein,[16] in discussing infant growth, has compared the new-born infant to a plant, because the first thing it requires is water. The average water content of the new-born is from 75 to 80 per cent. In order to conserve the necessary water for the growing tissue, the infant needs an average of 150 gm. of water per kilogram of body weight. He questions whether plants adapted to moderate moisture are not often disturbed when placed in soil that is excessively moist. Can not infant's growth be likewise influenced by excessive water intake? To this question he finds no ready answer. All proof of water causing any real disturbance in nutrition is wanting. In the author's experience, the percentage of growth and nutrition is higher when concentrated mixtures are prescribed, due to surplus calories. Human milk has a low protein content which is sufficient for the normal new-born infant, but it is too low to repair a congenital defect. He considers hydration one of the first acts of growing, in which each individual food component plays its own special part. Protein due to its colloidal nature furnishes the swelling substances, while the alkaline salts retain water

15. Fry, F. M.: Fixed Principles in the Feeding of Infants, Canad. M. A. J. **14**:503 (June) 1924.

16. Finkelstein, H.: Infant Feeding and Growth, Arch. Pediat. **41**:219 (April) 1924.

and produce an alkaline reaction in the body fluids. Although carbohydrates do not take part in the composition of cell protoplasm, they are responsible to a large degree for the retention of protein, salts and water. Water and solid cell constituents are kept together by some binding structure which prevents their separation. Reducing carbohydrates or salts does not retard the growth but causes a considerable fall in weight by drawing on food stored in the tissues. During the period of declination, the water output by urine and perspiration is distinctly increased. There are two distinct groups: hydrostable and hydrolabile infants; the latter condition may cause atrophy. In cases of hydrostability there seems to be some protecting substance in the cells which regulates the exchange of matter by cell colloids and the surrounding liquid. This prevents any pathologic change in the cell. In feeding hydrolabile infants, the alkaline salts should be diminished by giving diluted milk or preparations with reduced whey content to decrease the supply of colloidal forming matter.

Exchaquet [17] believes the danger of overfeeding is greatly exaggerated. Diarrhea is seldom encountered in breast fed infants even when large quantities of milk are given. The only complication he observed from this cause was eczema. Overfeeding in artificially fed infants is decidedly less serious than underfeeding. Insufficiency may be total, reduced or partial in some special element, such as salt or vitamin. Total insufficiency of food may be due to poverty, or failure to recognize symptoms of insufficient feeding. Underfed infants may not cry in a normal way or may seen satisfied and fall asleep immediately after nursing. Constipation, diarrhea, loss of weight, pallor, feeble pulse, subnormal temperature and alterations in the blood picture are known indications of underfeeding. The diagnosis may be confirmed by testing the effect of increased food, and by weighing the infant before and after each feeding for three consecutive days. In grave dehydration and low temperature, the infant should be placed in a warm bed with hot water bags, given saline enemas or sugar solution, and warm food. In severe diarrhea with dehydration and loss of weight, it is best to give one-half the number of calories for the actual weight, then slowly increase the amount to the normal requirement.

### ARTIFICIAL FOODS

Sweetened condensed milk and powdered milk, for the feeding of infants in the tropics, had been investigated by Deeks.[18] These canned

17. Exchaquet, L.: Insufficient Feeding of Healthy Infants and Its Dangers, Rev. med. de la Suisse **43**:777 (Dec.) 1923.

18. Deeks, W. E.: The Use of Sweetened Condensed, Evaporated and Powdered Milks for Feeding Infants in the Tropics, Am. J. Trop. Med. **4**:113 (March) 1924.

foods proved satisfactory for normal growth in 90 per cent. of the babies. The difference in fats and vitamins is made up by using cod liver oil and fresh fruit juices. The usual dilution of sweetened condensed milk is in a ratio of 1 to 3, the dilution varying according to the weight of the child. In using milk powder the sugar is dissolved in warm water before the powder is added. When fresh milk is not available, this method is a suitable substitute.

In considering the use of albumin milk, Stransky and Tavs [19] discuss the experimental foundation of Finkelstein's protein milk. They studied the action of albumin milk, to determine whether the effect is due solely to calcium caseinate. Calcium caseinate is only a temporary substance, which may be split up at a very much lower temperature than that which occurs in the course of "lab" ferment. It consists of two phases: (1) precipitation of the casein with a simultaneous calcium fixation, and (2), a proteolytic action not unlike pepsin, which is capable of splitting off considerable nitrogen from the casein. They find that "lab" ferment increases the protein function of pepsin. If milk is given in a finer coagulated condition, the "lab" action is almost immediate.

Freudenberg and Stern [20] have also considered protein digestion in the infant, especially tryptic digestion with duodenal fluid. They found no difference in digestion whether breast milk or other forms of milk were used. The old theory that protein is difficult to digest now seems unreasonable.

Eckert [21] studied the effect of increased protein concentration in eight normal children fed on a proprietary milk preparation. The amount of protein was measured by the nem value, which is normally 10 per cent.; this was increased to from 30 to 40 per cent. The corresponding amount of sugar was replaced by lactalbumin. There was always a decrease in weight without any indication of disease. With high protein feeding the stools were often foul and contained mucus, but on returning to the original feeding there was an increase in weight. A decrease in weight on a high protein diet is due to poor assimilation and copious stools.

Dorlencourt and Spanien [22] find that fats are not well tolerated, although they seem to be digested. Casein digestion is more or less imperfect, which is proved by the abundant ammonia produced in the

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19. Stransky, E., and Tavs, L.: Albumin Milk. II. The Action of Lab Ferment, Jahrb. f. Kinderh. **107**:129 (Oct.) 1924.

20. Freudenberg, E., and Stern, A.: Protein Digestion in the Infant, Jahrb. f. Kinderh. **106**:109 (June) 1924.

21. Eckert, M.: The Effect of Increased Protein Concentration in the Feeding of Infants, Ztschr. f. Kinderh. **37**:1, 1924.

22. Dorlencourt and Spanien: Modifications in the Digestion of Casein Produced by Milk Fats, Bull. Soc. de pédiat. de Paris **22**:282 (June-July) 1924.

intestine. In experiments made in vitro, the digestion of casein is not impeded by additional fats in ample quantity. Casein indigestibility in the intestine of infants fed on sweet milk is due to a complex condition, and warrants further study.

Struthers,[23] Gleich,[24] Field,[25] Mulherin,[26] and Marfan[27] and his co-workers have considered the use of acidified milk, particularly for young infants with nutritional disturbances. It is of special value in the treatment of marasmus, when it may be fed with much stronger mixtures than sweet milk. Observations were made on the weight, stools, disposition, sleep, skin, abdominal distention and vomiting. The average number of calories per kilogram of body weight was 196, and the average gain in weight was 8 ounces per week. This preparation affords an excellent means for treating athreptic infants and may be given in concentrated feedings, which overcomes much of the vomiting. Acidified milk is apparently well digested by premature infants. Field,[25] in a study of seven healthy infants, used acidified milk exclusively for 282 days, yielding an average daily gain of 1.3 ounces. Mulherin[26] advises adding 1 ounce of Karo syrup by volume to the acid milk, because this is more difficult to ferment. These authors all agree that lactic acid feeding cannot be used as a panacea for infant disturbances.

In a special study of the duodenal contents, after the administration of acidified milk mixtures, Schiff and Gottstein[28] find that the acid reaction prevents bacterial fermentation of carbohydrates and the consequent development of volatile fatty acids. After the administration of acidified milk, the acid of the duodenum increases in a half hour and persists for one hour. Buttermilk produces no increase in the acidity of the infant's duodenal content. Experiments made on dogs, after the ingestion of a neutral food, showed that the duodenal contents had an acid reaction. After the administration of an acid food the duodenal content became alkaline, especially in the lower third of the jejunum in which it was strongly alkaline. This work demonstrates that acid food does not necessarily produce an acid reaction of the duodenal contents, and that the capacity for the killing of colon bacilli cannot solely be attributed to buttermilk.

23. Struthers, R. R.: The Use of Acid Milk Mixtures in Infant Feeding, Canad. M. A. J. **14**:713 (Aug.) 1924.

24. Gleich, M.: Experiences with Lactic Acid Milk in Infant Feeding, Arch. Pediat. **41**:548 (Aug.) 1924.

25. Field, M. C.: A Clinical Study of Lactic Acid Milk as a Routine Feeding for Sick and Healthy Infants, Arch. Pediat. **41**:541 (Aug.) 1924.

26. Mulherin, W. A.: Acidified Milk with Karo Syrup as an Infant Food, J. M. A. Georgia **13**:287 (July) 1924.

27. Marfan, A. B.; Turquety, R., and Aris: The Use of Buttermilk for Feeding Debilitated New-Born Infants, Paris méd. **14**:353 (Nov. 1) 1924.

28. Schiff, E., and Gottstein, W.: How Does the Acidity of the Duodenal Contents Behave on the Administration of Acid Milk Mixtures, Jahrb. f. Kinderh. **107**:99 (Sept.) 1924.

In a detailed study of the digestion of fresh and sour cow's milk, Jensen and Spur [29] point out the importance of using acidified milk when one considers the buffer action of cow's milk. The sourer the milk the more easily will it be digested by the pepsin of the stomach. This especially applies to infants whose gastric juice contains too little hydrochloric acid. They find that the rate at which milk is digested varies with different strengths of hydrochloric acid.

### BUTTER FLOUR FEEDING

In reporting their experience with the Czerny-Kleinschmidt butter flour mixture, Schumacher,[30] Wisch,[31] and Greenwald [32] are convinced that butter flour is of value in feeding feeble and premature infants as well as healthy ones. The best results were obtained with a mixture of natural and artificial food. In cases of malnutrition due to some wasting disease, such as tuberculosis or syphilis, this feeding is of little help. It is usually disastrous in chronic indigestion as the tolerance for fat is much below normal. For children with acute nutritional disturbances manifested by diarrhea, fever and loss of weight, the high fat feeding seems to intensify the condition.

In a detailed study of flour digestion, Simchen [33] calls attention to the fact that a few years ago infants were not given flour. He quotes the work of Ibrahim who demonstrated that even a new-born infant produces a starch ferment. In considering the question of starch digestion Simchen [33] found that the capacity increases with age. In intestinal diseases the digestion of starch often suffers first, and is more marked the younger the child. Starch assimilation is difficult, and absorption depends on the length of time the starch remains in the intestine.

Göttche [34] has noted the antidyspeptic action of butter flour gruel for changing a fermentation in the intestinal tract into a putrefaction. In seventy infants without atrophy this diet had an excellent antidyspeptic action. The increase in weight was slow, but stable. By concentrating the food, this investigator obtained a decided advantage

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29. Jensen, O., and Spur, B.: The Digestion of Fresh and Sour Cow's Milk, Ugesk. f. Laeger **86**:655 (Sept. 4) 1924.

30. Schumacher, P.: The Value of Czerny-Kleinschmidt Butter Flour Feedings for Feeble and Healthy New-Born Infants, Arch. f. Gynäk. **122**:479 (July 1) 1924.

31. Wisch, L. J.: Some Observations on the Czerny-Kleinschmidt Butter Flour Mixture, J. Indiana State M. A. **17**:116 (April 15) 1924.

32. Greenwald: The Value of the Low Fluid Content of the Butter Flour Mixtures, Arch. Pediat. **40**:812 (Dec.) 1923.

33. Simchen, H.: Studies of Flour Digestion in the Infant, Arch. f. Kinderh. **75**:6 (Sept.) 1924.

34. Göttche, O.: An Anti-Dyspeptic Modification of Moro's Butter Flour Whole Milk, Orvosi hetil. **63**:357 (Aug. 24) 1924.

in parenteral infection and in spastic vomiting. In no instance, even after prolonged administration of the diet, was an injury noted from the lack of fluid intake.

### PERISTOLIC FUNCTION

The most important advance in determining the genesis of habitual vomiting has been demonstrated by Rogatz [35] in a series of papers appearing during the last year. These papers embrace some careful experiments made in Finkelstein's clinic by using the fluoroscope in association with infant feeding. Rogatz was able to illustrate the function of the stomach on the following feedings: (1) average milk formula of fluid consistency; (2) concentrated gruel, and (3) a very thick food of cereal and water or mashed potato and vegetable. Each examination was started from three to four hours after the last meal to insure an empty stomach. He found that the infant's stomach reacts differently to fluids and to semisolids. When fluids are given, the stomach assumes either a pear or oval shape, horizontal in position, extending beyond the middle with a large air bubble. With food that is very thick, the infant's gastric organ contracts down to a small circular shape, barely reaching the middle line and never extending beyond it, with little or no air bubble present. The air bubble varies in size, shape and form in all stomachs with fluid contents, but is distinctly smaller or often absent when thick gruels are swallowed. This study and demonstration of the peristolic function has an important practical significance in the treatment of pylorospasm and habitual vomiting. In patients who swallow a great deal of air with cereal, as sometimes happens, the muscular action of the stomach markedly contracts with the expulsion of air. This is especially true when the food is thick and when it is grasped and retained by the stomach. Thick food is less mobile than fluid, and offers a welcome resistance to the gastric musculature. These facts prove the necessity of more concentrated food in place of fluid feeding.

Crasson [36] described the use of thick cereal in the treatment of malnutrition. He has used it in pylorospasm, after the use of protein milk, or in premature infants in whom smaller quantities of concentrated feeding are needed. His method is to make up a simple whole milk formula, and to replace the sugar with from 4 to 7 tablespoonfuls

35. Rogatz, J. L.: Roentgenologic Studies on the Peristaltic Function of the Stomach in Infancy, and Its Significance in the Genesis of Habitual Vomiting, Ztschr. f. Kinderh. **38**:1 (April 5) 1924; Roentgen-Ray Studies of Stomach Function, Am. J. Dis. Child. **28**:53 (July) 1924; Roentgen-Ray Studies of Stomach Function: The Peristolic Function, Am. J. Dis. Child. **28**:69 (July) 1924; The Peristolic Function. Its Practical Significance in Cases of Pylorospasm and Habitual Vomiting, Am. J. Dis. Child. **28**:582 (Nov.) 1924.

36. Crasson, R. J.: Thick Cereal Feeding in Malnutrition Cases, Arch. Pediat. **41**:258 (April) 1924.

of rice or farina. This is cooked with the milk formula for fifteen minutes in a double boiler. For all children on thick cereal feeding, orange juice should be added to the diet; with older infants fresh green vegetables should be added.

Marriott [37] gives the malnourished infant more calories per kilogram of body weight than it requires, but, unfortunately, it has a diminished digestive capacity. Attempts to meet the caloric deficiency by the use of ordinary sweet milk or cream mixtures have rarely been successful. Breast milk is more satisfactory, but even this may be insufficient to supply the necessary number of calories. Cow's milk acidified with lactic acid and enriched by corn syrup will sometimes make up the caloric requirement. However, with all these variations of feeding, some malnourished infants fail to gain weight. It is then necessary to resort to some other method for increasing the capacity to absorb food. Two methods are proposed by this author: (1) repeated transfusions of matched citrated blood, 20 c.c. per kilogram of body weight, and (2) a 20 per cent. solution of glucose injected slowly into the vein in amounts of from 20 to 30 c.c. per kilogram of body weight, combined with 15 units of insulin per hundred cubic centimeters. A gain in weight invariably occurs, which is not lost when the injections are discontinued.

### METABOLISM

Talbot,[38] in a general survey of infant metabolism, considers that there is an increase of from 30 to 40 per cent. in twenty-four hours with muscular activity. The basal metabolism of premature infants is quite low compared with that of normal infants. With increasing age and weight there is an increase in heat production. Probably the changing condition of metabolism corresponds directly to the function and size of the thyroid.

In a study of the metabolism in undernourished infants, Fleming and Hutchison [39] consider as causes of failure to gain: (1) defective absorption of food, (2) defective utilization of absorbed food in the tissue, and (3) excessive combustion of absorbed food. Observations were made on four healthy and eight marasmic children; no child showed a defect in the power to absorb fat. In six cases the nitrogen balance, irrespective of whether the weight was rising or falling, was positive. It was found impossible to estimate the absorption of carbohydrate. Incomplete utilization of food may occur as the result of

37. Marriott, W. McK.: The Food Requirements of Malnourished Infants with a Note on the Use of Insulin, J. A. M. A. **83**:600 (Aug. 23) 1924.

38. Talbot, J. B.: Basal Metabolism in Infants, Monatschr. f. Kinderh. **27**: 465 (Feb.) 1924.

39. Fleming, G. B., and Hutchison, H. S.: A Study of the Metabolism in the Undernourished Infant, Quart. J. Med. **68**:339 (July) 1924.

defective or increased oxidation. Failure to oxidize absorbed foods does not play a part as a cause of marasmus. Determinations of basal metabolism show that undernourished infants, after they become 35 per cent. underweight, have a lowered basal metabolism. It seems likely that marasmus is not caused by metabolic disturbances, but that any alteration in the basal metabolism is due to emaciation accompanying the undernourishment.

Wang, Witt and Felcher,[40] and Wang and Davis [41] have been unable to find any metabolism studies that have been made by using breast milk and cow's milk with the same infant as the subject. They fed alternately with breast milk and modified cow's milk; six days on each diet. An analysis was then made on the calcium, phosphorus and chlorin content of both urine and feces. On the first three days of each period no specimen was collected, thus giving the child an opportunity to become adjusted to the change from one milk to the other. A change from breast milk to cow's milk, or vice versa, was invariably accompanied by a change in the amount of calcium as excreted in the feces. The actual quantity was always greater on a diet of cow's milk. Calcium absorption and retention run parallel, since the variation in the urinary calcium output is slight and of little significance. The amount of calcium absorbed and retained is greater for cow's milk than for breast milk, but the percentage of utilization and retention is greater for breast milk. The results of these observations show that changes in diet from breast milk to cow's milk are frequently followed by an increase of the chlorid excretion in the feces and urine. The utilization of chlorid runs parallel to the urinary chlorid; with breast milk it is somewhat lower than with cow's milk. There is no marked difference in percentage utilization of chlorid intake between the two. Changes of milk have no effect on the chlorid content of the blood. On a diet of breast milk or cow's milk, the average blood chlorid per hundred cubic centimeters of plasma varies only 10 mg.

In a series of water economy tests in hydrolabile children, Block [42] finds that the water elimination in hydrolabile children is far in excess of the normal, with increased instability. Combined water and carbohydrate tests do not differ from the ordinary water tests in hydrolabile subjects. It is a significant fact that hydrolabile children possess an ability for storing water which retains the water in the tissues. Block describes a method of experiment and the basis of this test.

70 East 77th Street.

40. Wang, C. C.; Witt, D. B., and Felcher, A. R.: A Comparison of the Metabolism of Some Mineral Constituents of Cow's Milk and of Breast Milk in the Same Infant, Am. J. Dis. Child. **27**:352 (April) 1924.

41. Wang, C. C., and Davis, L. H.: A Comparison of Some Mineral Constituents of Cow's Milk and of Breast Milk in the Same Infant. II. Chlorid Metabolism, Am. J. Dis. Child. **27**:569 (June) 1924.

42. Block: Experiments on the Water Economy in Hydrolabile Children, Ztschr. f. Kinderh. **38**:22 (April 5) 1924.

# Abstracts from Current Literature

## Anatomy and Physiology

THE NORMAL RHYTHM OF THE WHITE BLOOD CELLS. F. R. SABIN, R. S. CUNNINGHAM, C. A. DOAN and J. A. KINDWALL, Bull. Johns Hopkins Hosp. **37**:14, 1925.

This work is practically a monograph on the physiology of the white blood cells. It is too long to give an adequate abstract here. The bibliography is complete.

The authors summarize their work as follows:

1. There is a characteristic rhythm of the total white blood cells with an interval of approximately an hour's duration.

2. The total number of the white blood cells varies in the proportion of 1 to 2.

3. The total number of the white blood cells is increased in the afternoon regardless of whether food has been taken or not, and this entire increase is the result of an increase in the number of the neutrophilic leukocytes.

4. The neutrophilic leukocytes die out in showers, often of considerable proportions. These dead cells are promptly replaced, though whether from some reservoir or directly from the bone marrow, we have not yet determined.

5. The lymphocytes have a shorter rhythm than the leukocytes, but their total number varies in the proportion of 1 to 3, in contrast to the variation of 1 to 2 for the leukocytes.

6. A small proportion of the monocytes are normally undergoing division in the circulating blood.

7. In the five out of six apparently normal persons, small percentages of myelocytes were found in the circulating blood.

LYTTLE, New York.

THE REDUCING SUBSTANCES OF THE BLOOD. ALMA HILLER, G. C. LINDER and D. D. VAN SLYKE, J. Biol. Chem. **64**:625, 1925.

There are other substances beside glucose in the blood which reduce copper or ferricyanid in methods of blood sugar analysis. When glucose from blood was removed by fermentation or by incubation at 38 C., it was found there were reducing bodies still present in the blood, equivalent to from 0.01 to 0.03 per cent. glucose. Two out of six rabbits, which received large doses of insulin, were found to have no fermentable sugar in the blood, while the nonfermentable reducing bodies were normal in amount.

In four cases of glomerular nephritis the blood sugar determination gave high values; it was found that the increase was due to fermentable sugar, presumably glucose, while the amount of nonfermentable reducing substances were normal.

THE FATTY ACIDS IN THE SUBCUTANEOUS FAT OF MAN. H. C. ECKSTEIN, J. Biol. Chem. **64**:797, 1925.

Human fat removed from the abdomen of an obese individual at operation was available for study. The ratio of unsaturated fatty acids to saturated fatty acids was found to be essentially the same as that found by Bloor for blood lipoids and fecal lipoids, or 63.6: 26.6. This is in line with the belief that fecal fat represents fat excreted from the animal organism and not unabsorbed fat from the food; 0.24 per cent. cholesterol was found in cutaneous fat.

Fatty acids with 2, 3 and 4 double bonds were found—this differs from the statement of Bloor that it is rare to find in inactive fat of warm blooded animals any acid less saturated than oleic acid.

HIGGINS, Cincinnati.

THE SUGAR CONTENT OF BLOOD IN NORMAL AND UNDERNOURISHED CHILDREN AND THE EFFECT OF FAT ON THE ABSORPTION OF CARBOHYDRATE. MURIEL J. BROWN, Quart. J. Med. **18**:175 (Jan.) 1925.

This study was an attempt to determine whether absorption of carbohydrate is at fault in infants who are undernourished from any cause. The method employed was the determination of the blood sugar curves after ingestion of glucose to the amount of 1 gm. per kilogram of body weight. It was found that these curves were within normal limits, except in cases of pyloric stenosis in which, as might be expected, absorption was delayed. The author is aware that a normal curve does not necessarily mean that absorption is normal, because of other factors concerned with storage and oxidation that could not be controlled. The addition of 8 per cent. fat to the glucose solution did not alter the blood sugar curves. The results with fasting blood sugar, by which the author apparently means determination made four hours after food, confirms the findings of other authors that the blood sugar tends to be lower than normal in undernourished infants, especially in those who vomit.

JOSEPHS, Baltimore.

## Pathology, Bacteriology and Biochemistry

STUDIES IN CALCIFICATION. II. DELAYED EQUILIBRIUM BETWEEN THE CALCIUM PHOSPHATES AND ITS BIOLOGICAL SIGNIFICANCE. L. EMMETT HOLT, JR., VICTOR K. LA MER and H. BRUCE CHOWN, J. Biol. Chem. **64**:567, 1925.

The authors by chemical studies have found that blood serum is normally more than 200 per cent. supersaturated with tribasic calcium phosphate ($Ca_3[PO_4]_2$). This calcium phosphate would be precipitated under two conditions, (*a*) in tissues in which some agent is present to accelerate precipitation, and (*b*) in which actual contact is made with solid calcium phosphate. This latter condition is fulfilled in the body tissues bathing the bone matrix.

The maintenance of the supersaturation of the blood with calcium phosphate is very necessary for the prevention of tetany.

STUDIES IN CALCIFICATION. III. A QUANTITATIVE STUDY OF THE EQUILIBRIA CONCERNED WITH THE CALCIFICATION OF BONE. L. EMMETT HOLT, JR., J. Biol. Chem. **64**:579, 1925.

In 1922, Howland and Kramer offered as the criterion for determination of the activity of a rachitic process "The milligrams Phosphorus x milligrams

Calcium per 100 c.c. blood serum." When this product was less than 40, some degree of active rickets was present. Holt presents the ion product $[Ca^{++}]^3 \times [PO_4^{---}]^2$ as a more active criterion of the rate of deposition of $Ca_3(PO_4)_2$ and hence of the activity of rickets.

The author suggests that calcification is not completely arrested in rickets, but that it is so retarded that bone growth exceeds it in rapidity. Thus the inadequately calcified osteoid tissue, so characteristic of rickets, is produced.

HYPERGLYCEMIA PRODUCED BY GLYCEROL. CARL VOEGTLIN, J. W. THOMPSON and EDITH R. DUNN, J. Biol. Chem. **64**:639, 1925.

Glycerin in a 50 per cent. solution was given intraperitoneally or by mouth to rabbits. There was a resultant increase in the blood sugar. While there may be some other reducing substance such as glyceric aldehyd which caused this increase, the authors feel that it represents a conversion of glycerin into glucose.

ON THE RELATION OF THYROID SECRETION TO SPECIFIC DYNAMIC ACTION. EMIL J. BAUMANN and LOUISE HUNT, J. Biol. Chem. **64**:709, 1925.

The increased heat production following ingestion of glucose (specific dynamic action) by fasting rabbits was found to diminish gradually after the animals had their thyroid glands removed. After about sixty-five days, the specific dynamic action had disappeared; this was restored when the animals were fed desiccated thyroid gland. Incomplete thyroidectomy caused a decrease in the specific dynamic action, which was increased again by feeding thyroid and in some cases by feeding small amounts of potassium iodid.

BLOOD SUGAR TIME CURVES FOLLOWING THE INGESTION OF DIHYDROXYACETONE. I. M. RABINOWITCH, J. Biol. Chem. **65**:55, 1925.

Dihydroxyacetone is chemically a three carbon atom sugar (triose) which is easily polemerized into a hexose (glucose). Dihydroxyacetone in quantities of 25 to 100 gm. was fed to normal persons and to diabetic patients; the blood sugar in practically every case showed either no change or a decrease. As no dihydroxyacetone appeared in the blood, the author believes it had been changed into a hexose. He suggests that dihydroxyacetone may be of clinical value in diabetes because it has an insulin-like action in reducing blood sugar and is more readily tolerated than glucose. Clinical observations on the use of dihydroxyacetone in diabetes are promised in a subsequent article.

AN EXTRACT OBTAINED FROM THE EXTERNAL BOVINE PARATHYROID GLANDS CAPABLE OF INDUCING HYPERCALCEMIA IN NORMAL AND THEREOPARATHYROPRIVIC DOGS. A. M. HJORT, S. C. ROBISON and F. H. TENDICK, J. Biol. Chem. **65**:117, 1925.

The investigators have experimented with numerous methods of extracting the active principle from bovine parathyroid glands which will relieve tetany and induce hypercalcemia. An aqueous, dilute hydrochloric acid was the preferable medium for extraction. Removal of proteins from the extract did not reduce its potency. The hormone will last for over sixteen months in an icebox without loss of any of its activity. Dogs were found to vary in their susceptibility to the parathyroid extract, a fact which renders an assay of a preparation difficult.

THE LOSS OF BASES IN DIURESIS AND ITS EFFECT ON THE ALKALI RESERVE OF THE BLOOD. BYRON M. HENDRIX and DEA B. CALVIN, J. Biol. Chem. **65**:197, 1925.

It was found that diuresis, produced by intravenous injections of sodium nitrate, sodium chlorid, sodium sulphate, or urea, results in the loss of alkali reserve of the blood and corresponding excretion of base in the urine. The authors believe that the speed of the passage of urine through the tubules of the kidney is too great to allow the cells to absorb the base properly.

HIGGINS, Cincinnati.

EFFECT OF PREPUBERTY CASTRATION ON SUBSEQUENT CANCER IMPLANTATION. JAMES B. MURPHY and ERNEST STURM, J. Exper. Med. **42**:155, 1925.

The effect of gonadectomy on the susceptibility of animals to transplanted tumors has been a disputed subject. The gathering of information on the general reactions of the body to prepuberty castration seems important.

The authors found that: Male and female mice castrated during the first 7 weeks of life show a definitely higher resistance to cancers implanted at a later period than do intact mice of the same age. This increased refractiveness is evident at 3 months after castration, but is more pronounced at 8 months to 1 year. Even castration in early adult life seems to cause an increased refractory state to later cancer inoculation. On the other hand, adult mice inoculated with cancer within a week after castration show slight if any evidence of increased resistance.

MCCLURE, Evanston, Ill.

DIPHTHERIA IMMUNITY. M. J. ROSENAU and G. HOWARD BAILEY, J. Infect. Dis. **37**:97 (Aug.) 1925.

Experiments were performed to determine whether avirulent diphtheria bacilli are able to stimulate antitoxin production and thus account for the acquired immunity to diphtheria which most persons develop with maturity. Seventeen different strains of avirulent cultures and also cultures of related organisms, such as *B. hofmanni* and *B. xerosis,* were injected into guinea-pigs over a long period of time. The Schick test remained positive for all these guinea-pigs, and when the final test was made they showed no immunity to diphtheria toxin. It was found that there is considerable individual variation in guinea-pigs so far as their response to injections of diphtheria toxin is concerned. Usually the Schick test becomes negative for guinea-pigs in three months, and they then are immune.

These studies emphasize the essential difference between the so-called avirulent diphtheria bacilli and the true Klebs-Loeffler organism. Not only did the avirulent strains fail to induce immunity, but their agglutination reactions showed that there is a wide immunologic gap separating them from the diphtheria bacillus. Some of these so-called avirulent strains have pathogenic properties. A few of the guinea-pigs that received repeated massive injections of live cultures developed disseminated focal lesions, which are being studied.

No change in virulence was observed in cultures of avirulent diphtheria bacilli, in *B. hofmanni* or in *B. xerosis* under observation for eighteen months, and transferred for thirty-six generations on Loeffler's blood serum.

Guinea-pigs react with striking uniformity to the Schick test. All guinea-pigs appear to be like some children in that they are persistently positive. The guinea-pig's skin seems to be more sensitive than the human skin, for the typical reaction is produced by the intradermal injection of $\frac{1}{250}$ minimum lethal dose. Pregnancy and general systemic infections appear to inhibit the local skin reaction.

Pseudoreactions were not observed in these studies as a result of the injection of diphtheria toxin; but sensitized guinea-pigs responded to the injection of bacterial antigens, although this reaction is not specific. With certain bacterial extracts containing bacterial protein, a local necrotic action of the skin was produced which was interpreted as a modified Arthus phenomenon.

Experimental confirmation was obtained of the correlation between a positive Schick test and susceptibility and a negative Schick test and immunity. In a series of guinea-pigs it was found, furthermore, that a definite relation exists between the weight of the animal and the minimum lethal dose of diphtheria toxin. It takes about twice as much diphtheria toxin to kill a guinea-pig weighing four times as much as the standard control; in other words, if the minimum lethal dose for a 250 gm. guinea-pig is 0.011, it will take 0.022 for a guinea-pig weighing 1,000 gm.

Morphologically, the avirulent diphtheria bacillus resembles the true Klebs-Loeffler organism, but the results recorded emphasize the fundamental difference between the two groups, and throw doubt on the appropriateness of the name "avirulent diphtheria bacilli."

OBSERVATIONS ON D'HERELLE'S BACTERIOPHAGE. MAX S. MARSHALL, J. Infect. Dis. **37**:126 (Aug.) 1925.

The purpose of this work was the study of the phenomena of a d'Herelle type or strain of bacteriophage from a quantitative point of view, particularly as regards the mutual relationship between bacterial cells and bacteriophage. Studies of certain corollary features were also made from a quantitative point of view, specifically as regards the absorption of bacteriophage by bacterial cells, the diffusion of bacteriophage through agar and semipermeable membranes, the resistant strains and the lysed culture as antigen.

A technic was developed for the quantitative estimation of bacteriophage concentration, using an original type isolated by d'Herelle.

The normal rate of multiplication of Eberthella dysenteriae (Shiga) during the logarithmic phase of growth was determined, the rate of fission being once every 31.3 minutes in beef infusion broth at 37 C.

The effect of the bacteriophage on this normal logarithmic rate is such as to cause no variation from the normal for a greater or lesser period of time, depending on the concentrations both of the bacteriophage and of the organisms; following this there is a period of rapid lysis.

During this exposure of organisms to bacteriophage, a period of stability in bacteriophage concentration occurs, followed by a period of rapid increase, to some extent synchronous with the period of rapid bacterial lysis.

There was found to be a maximum concentration of bacteriophage in beef infusion broth, beyond which further lysis of bacterial cells seemed to cause no increase. This point of concentration was approximately 225,000,000 units per cubic centimeters.

Experimental results on cellular absorption of the bacteriophage showed the following:

1. Living bacterial cells sensitive to the lytic action of the bacteriophage absorb bacteriophage from a broth suspension within a period of fifteen minutes at 37 C. Dead cells of the same strain bring about progressive adsorption over a period of at least one hour. It was shown that such dead cells probably adsorb bacteriophage rather than absorb it.

2. Tests involving the absorption of bacteriophage by heterologous bacteria indicated absorption from a broth suspension within a period of fifteen minutes at 37 C. with some bacterial strains and none with others.

3. It is concluded that there is no specificity of bacteriophage absorption from the point of view of the accepted bacteriologic grouping, but that there is a specificity from the point of view of susceptibility to lysis by the bacteriophage.

The bacteriophage was found to diffuse 1 mm. in 2 per cent. agar in forty-eight hours, and to diffuse through parchmentized and collodion membranes. It is indicated that adsorption plays a rôle in the diffusion through parchmentized membranes.

Evidence is given to indicate a probability that the resistant or R. strains of the authors are combinations of normal cells, and older cells with a natural (possibly acquired) resistance, all associated with adsorbed and absorbed bacteriophage.

Attempts at adaptation of an antityphoid (Eberth) bacteriophage to a Rawling's strain of the typhoid bacillus were unsuccessful.

The use of typhoid culture subjected to lysis by bacteriophage as antigen in animal inoculation experiments did not result in a specific antityphoid serum when tested for the presence of agglutinins and precipitins against the normal antigens and the lysed antigen. Normal antityphoid immune serum, although having a high agglutinin concentration specific for the Eberth strain of the typhoid bacillus, was not found to have precipitins giving specific precipitation with bacteriophage-lysed Eberthella typhi (Eberth) antigen.

A discussion of the unity of structure of the bacteriophage is presented, and the theory that the agent responsible for transmissible bacteriolysis is a living ultramicroscopic entity is concurred in.

KENNEDY, Rochester, Minn.

PATHOLOGY OF "INTERNAL OR SPONTANEOUS CARBUNCLE." G. SANARELLI, Ann. d'ig. **4**:273, 1925.

The so-called internal or spontaneous carbuncle is regarded by most authors as an intestinal infection due to spores of bacteria ingested with the food. They escape the action of the gastric juice and proliferate in the intestinal tract. The pathologic picture of the lesions is that of the "internal malignant pustule."

Sanarelli's experiments in animals prove that after oral and rectal administration of spore-bearing and nonspore-bearing bacteria, the animals suffered no ill effects. The gastric and enteric juices effectively destroyed the organisms. This bactericidal action of the alimentary juice is easily demonstrated in vitro.

Some animals tolerate with impunity quantities of organisms far above the lethal dose. The animals succumbing to the treatment showed at necropsy that the septicemia resulted from infection through an abraded mucous membrane of the upper digestive passages.

Small quantities of enteric juice added to broth favored the growth of the culturable intestinal microbes but inhibited the growth of the "carbuncle" spores.

The spores when taken by mouth are often aspirated into the respiratory system, and are demonstrable in the lungs after twenty-four hours. Sublethal doses of spores entering the lungs are well resisted. Larger amounts cause a fatal septicemia.

Intestinal lesions may be produced by subcutaneous inoculations. The lymphatic patches of the intestines are the seat of infection.

Sanarelli believes that the lesions apparently due to direct ingestion of spores into the digestive tract are of hematogenous rather than enterogenous origin.

STUDIES ON INFLUENZA. G. VOLIPINO, Ann. d'ig. **4**:344-347, 1925.

In a previous paper (1922-1923), the author reported that the sputum of patients suffering from influenza, when preserved in glycerin and then injected subdurally into rabbits, produced an amicrobic type of encephalitis.

In 1924, there was a severe epidemic of influenza in the city of Messina. Volpino repeated his former experiments and his earlier results were confirmed.

Microscopically, the brain lesions of the acute type showed accumulations of polymorphonuclear leukocytes and mononuclear cells around the pia arachnoid and perivascular spaces. Inclusion bodies within endothelial cells were abundant in the neuroglia tissue and perivascular spaces. They were rarely seen within the nerve cells. They measured from 2 to 5 microns and stained red by Mann's method. The center appeared vacuolated.

In the subacute form there was considerable round cell infiltration of the meninges and perivascular structures. Nerve tissue degeneration was prominent. The inclusion bodies in this form of encephalitis were larger, more granular and less abundant than in the acute type. They did not stain well by Mann's method. The subacute process was markedly that of degeneration and destruction of tissue.

Volpino also found the same inclusion bodies in the sputum of the influenza patients. Analogous bodies were also demonstrated in the lung tissue.

Stained by Gram's method they retain a violet tint. This author also found that when preparations were stained by the Gram technic, many bodies were found extracellularly as well as intracellularly.

ZAMBARANO, Northville, Mich.

THE USE OF THE SYNTHESIS OF HIPPURIC ACID IN DETERMINING RENAL FUNCTION. G. BIGNAMI, Arch. di patol. e clin. med. **3**:592, 1924.

Benzoic acid and its salts are excreted in the urine as hippuric acid; this excretion amounts to 100 per cent. of the intake in six hours, providing the kidneys are normal. The consensus of opinion among investigators is that the kidneys play the main rôle in the synthesis of hippuric acid in the body. The author, therefore, has used the excretion of hippuric acid as an index of the kidney function.

The test consists of the giving of 2.4 gm. of sodium benzoate by mouth; urine is collected in two 3 hour periods and its hippuric acid content is determined. When there is an impaired kidney function, the excretion of hippuric acid is diminished. The test gives results comparable to those obtained by the phenolsulphonephthalein test and by Ambard's quotient.

HIGGINS, Cincinnati.

EFFECT OF INSULIN INJECTION ON THE COMPOSITION OF MILK. EIKICHI KAMITANI, J. Pediat., Tokyo, p. 921 (June) 1925.

Kamitani experimented with two goats soon after they gave birth to kids. Insulin, distributed by the Cannaught Laboratories, was injected to the amount of 1 to 3 units per 2,000 kilograms of body weight and the milk was expressed at two hour intervals. The experiment demonstrated that the lactose in the milk showed a decrease of 17 per cent., and the duration of low carbohydrate was prolonged by increasing the dose of insulin. The acidity of the milk was also decreased at the same rate as lactose. The fat greatly increases in amount if the milk is expressed frequently, and the viscosity also increases proportionally. Giusti and Rietti once concluded that the milk fat is increased by insulin, but our experiment shows that the increase is not due to insulin. The effect of insulin on total nitrogen, calcium content, water and specific gravity is uncertain.

KATO, Los Angeles.

## Nutrition

LACTIC ACID MILK IN THE FEEDING OF PREMATURE CHILDREN. MORRIS GLEICH, Arch. Pediat. **42**:432, 1925.

Gleich's experience with the feeding of lactic acid milk has led him to express the belief that it furnishes an excellent substitute for breast milk in feeding premature babies. Furthermore, the presence of acid in the milk enables a premature child to tolerate a liberal supply of fat, which accounts in no small way for the gain in weight and general improvement. The author encourages the care of premature infants at home, rather than at a hospital, quite a departure from the routine. Cross-infection, which in an institution cannot be avoided, finds easy victims in these premature infants, and they soon succumb. A list of acid milks is appended, also a report of five cases.

VON MEYSENBUG, New Orleans.

FAT-SOLUBLE VITAMINS. XXIV. THE NONPRECIPITABILITY OF THE ANTI-OPHTHALMIC AND ANTIRACHITIC PROPERTIES FROM COD LIVER OIL BY DIGITONIN. E. M. NELSON and H. STEENBOCK, J. Biol. Chem. **64**:299, 1925.

The active principles of cod liver oil in preventing ophthalmia and rickets have been found in the nonsaponifiable constituents of the oil. There are many of these nonsaponifiable bodies, and prominent among them are the sterols — especially cholesterol and phytosterol. The sterols as a group are precipitated by digitonin. The authors in this manner removed sterols from cod liver oil. The cod liver oil deprived of sterols was quite as effective in preventing keratomalacia and rickets as the untreated oil. It would thus appear that the sterols are not the portion of cod liver oil containing the vitamins.

THE PHOSPHATID AND TOTAL PHOSPHORUS CONTENT OF WOMAN'S AND COW'S MILK. ALFRED F. HESS and F. DOROTHY HELMAN, J. Biol. Chem. **64**:781, 1925.

Phosphatids are the fatty or lipoid substances which contain phosphorus; the principal phosphatid is lecithin. Phosphatids are important factors in the structure and growth of the body; their rôle in the food is uncertain and debatable. However, as milk forms the important part of an infant's diet, it may be of some significance to know the phosphatid content of milk.

New methods for extraction of phosphatids and the determination of phosphorus should make the present results more accurate than any previously reported.

The results are given in the following table:

| Human Milk | Total Phos. Mg. Per 100 c.c. | Phosphatids Mg. Per 100 c.c. |
|---|---|---|
| Colostrum | 8.16 | 2.54 |
| Early nursing period (8 cases)* | 8.77 to 17.02 | 1.48 to 4.06 |
| Later nursing period (7 analyses) | 12.34 to 24.39 | 2.10 to 2.96 |
| Cow's Milk | | |
| Raw (7 samples) | 80.0 to 81.6 | 5.29 to 6.99 |
| Pasteurized (2 samples) | 7.59 | 5.33 to 6.5 |
| Skimmed 0.4 per cent. (2 samples) | 96.0 to 109.0 | 4.12 to 4.44 |
| Cream 32 per cent. fat (1 sample) | 64.9 | 10.25 |
| Cream 20 per cent. fat (1 sample) | 65.8 | 7.14 |
| Colostrum (2 samples) | 93.8 to 113.6 | 10.52 to 11.76 |
| Goat's Milk | | |
| 2 samples | 102.6 to 133.3 | 3.0 to 5.35 |
| Ass' Milk | | |
| 2 samples | 60.6 to 72.7 | 2.38 to 7.19 |

*Cow's milk contains about twice as much phosphatid as human milk. Skimmed milk contains a fair amount of phosphatid, but a larger proportion is in the cream.

IRON IN NUTRITION. I. NUTRITIONAL ANEMIA ON WHOLE MILK DIETS AND THE UTILIZATION OF INORGANIC IRON IN HEMOGLOBIN BUILDING. E. B. HART, H. STEENBOCK, C. A. ELVEHJEM and J. WADDELL, J. Biol. Chem. **65**:67, 1925.

Animals kept on a milk diet exclusively develop anemia as soon as the reserve supply of iron in the spleen and liver becomes exhausted. The addition of inorganic iron to the diet is insufficient to prevent the anemia, it being necessary that some substance containing the pyrrol group also be incorporated in the diet; this latter substance is most abundant in the green coloring matter of plants (especially chlorophyl).

The experimental work presented was done on rabbits. Rabbits developed anemia in about six weeks when on a diet of whole cow's milk, containing sufficient sodium citrate to prevent gastric indigestion. When ferric oxid was added to the diet, the anemia was neither cured nor prevented; when, however, green cabbage also was given, the anemia did not develop, or, if already present, was cured. Alcoholic extracts of cabbage, and of corn meal and also purified chlorophyl were made and found free of iron. Each of these substances was incorporated into the diet of milk and ferric oxid, and rendered the diet such that anemia was prevented or cured.

The authors believe that vitamin E, which is necessary for reproduction, may not be a real vitamin; the reported deficiency might be due merely to anemia from lack of the chlorophyl substance in the diet.

DIRECT PRECIPITATION OF CALCIUM IN COW'S MILK. CARMEN S. ROTHWELL, J. Biol. Chem. **65**:129, 1925.

The author has been able to determine accurately the calcium content of cows' milk by a direct precipitation method using ammonium oxalate; this method did not yield accurate results with human milk.

HIGGINS, Cincinnati.

REPORT OF TWO THOUSAND INFANTS FED ON DRY MILK. MATHER M. MCCORD, J. M. A. Georgia **14**:316, 1925.

McCord states that his experience with dry milk has been rather extensive, since he has had opportunity of observing it tried in approximately 2,000 infants extending over a period of six years. He first sought to understand dry milk, and then began to try it out on some of his difficult feeding cases. The results were most satisfactory from the beginning. In numerous cases in which he failed to get an undernourished infant to thrive on raw cow's milk, he was able to obtain a satisfactory response at once in the use of dry milk.

MASHBURN, Atlanta, Ga.

SOME PHOSPHORUS COMPOUNDS OF MILK. H. D. KAY, Biochem. J. **19**:433-445, 1925.

Two acid-soluble phosphorus compounds in organic combination are present in cow, goat and human milk, one compound hydrolyzable by dilute acids and by extracts of tissues and one being more stable. The former contains 4.4 mg. per hundred cubic centimeters of protein in cow, 13.3 mg. per hundred cubic centimeters in goat and 3.3 mg. per hundred cubic centimeters in human milk. Both compounds diffuse readily through collodion membranes.

THE PERSISTENCE OF VITAMIN A IN PLANT TISSUES. KATHERINE H. COWARD, Biochem. J. **19**:500-506, 1925.

Vitamin A is not used up in any process carried on by living plant tissue in darkness. It is increased when the leaf loses its green color and becomes yellow. It is completely destroyed when the leaf dries and dies.

KUGELMASS, New York.

THE MILK SUPPLY OF THE COUNTRY AND ITS BEARING ON HEALTH. Discussion, ROBERT PHILIP, J. F. TOCHER, J. T. MACKIE and others, Edinburgh M. J. **32**:89 (May) 1925.

This discussion was held before the Medico-Chirurgical Society of Edinburgh, and deals with the regulation of the production and distribution of milk in Scotland. It is interesting to note that there are nine producers of certified milk in England and an equal number in Scotland. Tocher writes of the variations in the composition of cow's milk, and the factors which influence them. Mackie discusses the presence of tubercle bacilli and the bacterial content of milk as the factors of greatest importance in infancy. He recommends sterilization or pasteurization as a vital necessity and believes that milk should be so treated before distribution and sold in sealed sterilized bottles.

NEFF, Kansas City, Mo.

THE SPECIFIC DYNAMIC ACTION OF FOOD. CARLO BARINETTI, Arch. di patol. e clin. med. **4**:201, 1925.

Barinetti determined the basal metabolism and the effect of food on the basal metabolism of essentially normal individuals and of patients with endocrine disturbances. Following the ingestion of 160 gm. of bread, 160 gm. of meat and 10 gm. of butter, there was normally an increase of about 20 per cent. in the metabolism; it is ascribed to the specific dynamic action of the food. When a suspension of barium sulphate was fed, the metabolism increased about 6 per cent.; this increase was due to peristalsis.

The specific dynamic action from the foregoing diet was essentially normal in cases of exophthalmic goiter, of infantilism and of acromegaly. However, in one case of hypothyroidism and several of obesity, there was no increase in the metabolism following food. In the obese patients, the injection of hypophysin, an extract of hypophysis, caused the appearance of a specific dynamic action from food, while thyroid gland tablets did not do so.

HIGGINS, Cincinnati.

AN EXPERIMENTAL STUDY OF THE EFFECT OF PEPPERMINT, FENNEL AND CHAMOMILE TEAS ON THE GASTRO-INTESTINAL TRACT. W. ARNOLD, Monatschr. f. Kinderh. **30**:225, 1925.

As household remedies the teas mentioned in the title have been used for many years. Very little is known, however, of their real pharmacology.

Arnold gave barium meals to children and then by repeated roentgen-ray and fluoroscopic examinations determined the effect of these infusions on gastro-intestinal motility. The meals were identical, were given at the same time of day and the children were kept under identical conditions.

There is no question that these drugs do affect the gastro-intestinal tract. They quiet and relax the stomach while they seem to have a stimulating effect on the intestine, especially the large bowel. In this action peppermint seems to be the most active with fennel as second. There is an excellent reason that these drugs have been used by the laity for the colic of infants these many years.

PATHOGENESIS OF CARPOPEDAL SPASM. OTTO BOSSERT, Monatschr. f. Kinderh. **30**:253, 1925.

This is an interesting clinical study of a number of cases of latent tetany. In some patients, sodium citrate in doses of 5 gm. was sufficient to produce carpopedal spasm. In others the syndrome developed following sudden fluctuations of weight. Further observations with sodium citrate showed that the dose given was sufficient to affect the weight and to produce some edema of the extremities.

Putting these facts together, Bossert argues that carpopedal spasm results from local changes in the tissues due to disturbance of the salt and water metabolism. Sodium citrate acts not by reason of its alkalinity but by producing this type of disturbance.

LOSS OF APPETITE IN CHILDHOOD. ST. ENGEL, Monatschr. f. Kinderh. **30**:270, 1925.

This is a good clinical description of the usual anorexia nervosa so well known to pediatricians. The children show the usual stigmas and reactions of the neuropath. Their taste in food is not for the simple and wholesome articles of diet but for the spicy, piquant and irritating, as if their appetite were maturing too early into the adult type. The treatment is well known. The ideal therapy is to remove the child from its environment, which means from a nervous mother, and to place it in the charge of a calm but firm nurse or relative.

GERSTLEY, Chicago.

## Prenatal Conditions

RELATIONSHIP OF NEONATAL MORBIDITY AND MORTALITY TO THE TOXEMIA OF PREGNANCY. I. A. ABT, Arch. Pediat. **42**:415, 1925.

An investigation was made of 210 mothers suffering from toxemia of pregnancy. Toxemia occurred more frequently in primiparous than in multiparous mothers. Thirty-nine infants were born dead; twenty-seven were stillborn; twelve were macerated. In the series eighty-two were born at full term, 122 were

more or less premature; in twenty cases the information was not obtained. Infants who were born of eclamptic mothers showed diffuse hemorrhagic areas and also anemic and hemorrhagic necroses in the various organs, which are similar to the changes found in eclamptic mothers. Blood and albumin have been found in the urine of these infants. Necrosis of the liver cells is sometimes observed. The neonatal mortality in the series was 24.77 per cent. The maternal eclampsia did not seem to effect a permanent injury in the infants who survived. Infantile convulsions occurred only five times, but it is to be remembered that many of the mothers who had convulsions gave birth to stillborn children shortly after the eclampsia. Congenital malformations occurred eight times. It is possible that maternal toxemia occurring early may favor fetal malformations. VON MEYSENBUG, New Orleans.

CONGENITAL MICROCOLON. DAVID M. GRIEG, Edinburgh M. J. **32**:175 (April) 1925.

This may be more frequent than reports in the literature would indicate. Grieg examined the specimens from three cases in the Edinburgh museum. The symptoms had been persistent vomiting from the first day of life, drawing up of the legs, no stools, rapid emaciation, palpable masses through the abdominal wall, abdominal distension, no tumor felt through the rectum. All three infants were operated on, and the colon was found firm and small. A cysticocolic ligament was present in one case, and a segment of the jejunum was absent in another. All three infants succumbed within a few days after operation.

Congenital microcolon is a miniature colon, with a lumen, the different layers of the wall proportionately normal, the mucosa has secreted its succus entericus, but no meconium is present. Grieg discusses the various causes assigned in the production of microcolon, and concludes that it is not an anatomic defect but a physiologic aberration.

The only hope is for early operation with the diagnosis clearly made. An anastomosis must be made proximal to the inspissated meconium in the ileum and the colon beyond the narrow segment.

The examination of the specimen, the discussion of this and allied obstructive conditions and the literature, are given with completeness.

MALDEVELOPMENT OF THE WRIST AND HAND. LAMBERT ROGERS, Edinburgh M. J. **32**:407 (Aug.) 1925.

A boy, aged 8 years, showed a curious maldevelopment of the left hand in that it resembled a foot. There were five little digital buds which looked like toes. Under the roentgenogram numerous deformities were found in the carpals, metacarpals and phalanges. The author discusses the normal reductions and fusions which occur in the bones of the hand. In this case, the number of bones is below the normal. NEFF, Kansas City, Mo.

## Diseases of the New-Born

SYPHILITIC HYDROCELE OF THE NEW-BORN. B. SPARACIO, Riforma med. **41**:462 (May 18) 1925.

Among the rare symptoms of hereditary syphilis, the inflammation of the vaginal membrane is most important. The hydrocele of syphilis is usually unilateral, persistent and irreducible. The author reports a case in a boy,

1 month old, who also had Parrot's disease of the right shoulder. Anti-syphilitic treatment cured both conditions.

PARDO CASTELLO, Havana.

CONTRIBUTION TO THE MECHANICS OF THE DEVELOPMENT OF HEMORRHAGES IN THE TEMPORAL BONE CAUSED BY INJURY DURING BIRTH. J. BERBERICH and M. STERN, Ztschr. f. Hals-, Nasen-u. Ohrenh. **11**:383 (July 20) 1925.

The great majority of births are head presentations (from 95 to 97 per cent.). The effects of injury to the skull of the child take a prominent place when considering birth injuries. In the older reports (Seitz, Beneke, Yllpoe and others), mechanical circumstances were considered especially the clipping off of parts, contusions, compressions, strangulation and injuries by forceps as a cause of changes in the skull (cephalehematoma, caput succedaneum, tears of the tentorium, pia and cerebral hemorrhages), Schwartz believes that cerebral hemorrhages of the new-born are mainly caused by the difference of the pressure in the uterus and in the atmposphere. It is known that an even pressure on all parts of the fetus exists when the amniotic sac is intact. The pressure amounts to from 80 to 250 mm. of mercury. At the moment when the amniotic sac bursts, the protruding portion of the fetus closes the open os uteri like a ball valve. The parts in the uterus are still subjected to the high pressure and a part of the body surface (in cranial presentations a part of the head) is suddenly relieved of this pressure. If we place on any part of the body a Biers suction bell, a swelling occurs corresponding to the power of suction, because the mobile fluids of the organism flow into that part of the organism which is freed from the ordinary pressure of the atmosphere. At the moment when the head of the fetus, after bursting of the sac, occludes the os uteri like a ball valve, the great difference in pressure between the uterus and the atmosphere causes that part of the body which lies outside the uterus to be exposed to an influence corresponding to that of a large Biers suction bell; the fluids of the body are drawn to the spot at which suction occurs. If this difference of pressure is continued sufficiently long, a hyperemia of the vessels in the suction region must occur and at last the vessels are torn. The caput succedaneum and cephalematoma can be explained in this manner.

It can easily be imagined that by sufficiently great suction of the veins of the scalp and of the longitudinal sinus not only these veins but the veins which stand in connection with the same and the sinus are filled with blood, and finally they tear. Schwartz explains in this manner the pial and the intercerebral hemorrhages. This view of Schwartz is corroborated by earlier investigations of Stumpf, Sicherer, Paul, Hippel and others, who found hemorrhages in the fundus of the eyes of the new-born. These authors looked on them to be distant effects of birth injury. Voss established a typical symptomatology of the birth injuries of the new-born. In numerous cases Voss could show hemorrhages histologically in the temporal bone of the new-born, which were the result of birth injury. Bruehl could show connection of the veins of the tympanic cavity with the superior petrosal sinus. Other authors (Ostmann, von Troeltsch), pointed out vessel connections between the middle ear and the cranial cavity. Berberich and Stern confined their studies only to the venous connections. Manasse, Politzer, Urbantschitsch, von Troeltsch, Siebenmann, Zange and Brieger did not only find vessel connections between the middle and the inner ear, but also with the superior and inferior petrosal sinuses. If, according to Schwarz, a congestion occurs in the longitudinal sinus the

stasis can take place through the long course of the longitudinal, transversal, and sigmoid sinuses or by the way of the short stretch of the anastomosis veins, the cavernous sinus and the inferior and superior petrosal veins, and it can extend to the smaller veins of the brain, the vena magna galens, vena cerebri interna, vena terminalis, vena cerebelli, vena lateralis ventriculi. Berberich and Stern made experiments by injections on the cadaver in order to make visible the venous connection between the longitudinal sinus and the temporal bone, respectively, of the brain. The cadavers of children and adults were used. If a strong pressure is used, it is possible to tear fine branches in the inner ear and the injected mass can be found in the endolymphatic and perilymphatic spaces. The authors conclude that:

1. The veins of the brain and of the temporal bone can be filled evenly to the smallest branches by injecting any kind of a fluid into the longitudinal sinus of the cadaver.

2. In this manner it can also be proved that the veins of the temporal bone belong to the great vessel system of the superior longitudinal sinus.

3. These investigations brought a further proof that hemorrhages in the petrous bone by birth injury (Voss) can develop by suction, with consecutive disturbance of the circulation in the superior longitudinal sinus, and in the venous vessel system which stands in connection with the same.

AMBERG, Detroit.

## Acute Infections

THE CRITICAL PRE-ERUPTIVE FEVER. HENRY HEIMAN, Arch. Pediat. **42**:447, 1925.

The author describes in detail, giving the symptoms, signs and course of the condition which has been given various names of roseola infantum, exanthem subitum, pseudo-rubella, critical three day fever of infants, suggesting the name "critical pre-eruptive fever" as being more descriptive.

VACCINE THERAPY — THE METHOD OF CHOICE IN THE TREATMENT OF WHOOPING COUGH. C. J. BLOOM, Arch. Pediat. **42**:485, 1925.

Bloom uses a vaccine composed of Bordet-Gengou bacilli and influenza bacilli, mixed in such proportion that 1 c.c. contains 5,000,000,000 of the former and 3,500,000,000 of the latter. It is prepared fresh within the month. For infants under 6 months he gives 0.2 c.c., 3 doses on alternate days; from 6 months to 1 year 0.5 c.c., 3 doses on alternate days. Children from 2 to 6 years, 1.2 c.c., 3 doses on alternate days. After thirteen years' observation and in consideration of the fact that the author has followed many plans of treatment and different combinations of vaccines, this therapy in the management of pertussis is found to be the most efficacious in all respects. As a preventive, less than 1 per cent. of those vaccinated have up to this time developed pertussis.

A CASE OF MENINGITIS CAUSED BY THE BACILLUS PARATYPHOSUS B. M. B. BRAHDY, Arch. Pediat. **42**:550, 1925.

Report of a case in a child, aged 13 months, of purulent meningitis due to the *B. paratyphosus B* starting with a slight gastro-intestinal disturbance. It is the first case reported in the English literature.

VON MEYSENBUG, New Orleans.

FAMILY PREDISPOSITION TO SCARLET FEVER. SELMA MEYER (DOZ.), and ERICH BURGHARD, Monatschr. f. Kinderh. **30**:313, 1925.

In a study of the type of scarlet fever occurring in 173 families, and in its course and complications, the authors attempted to ascertain if there was any influence that might be attributed to the family itself. The results of the study are somewhat disappointing. The writers submit many tables and cover about fifty pages, but so far as one can make out the influence of family is almost negligible as regards susceptibility, course, complications and prognosis. The essential factor is the individual constitution of the patient.

GERSTLEY, Chicago.

BLOOD PICTURE OF TYPHOID FEVER IN CHILDREN. KUNIO TANAKA, J. Pediat., Tokyo, p. 1036 (July) 1925.

In thirty-six cases of typhoid fever in children, Tanaka found the following facts: (1) Neutrophils change in the same manner as in adults, but in children of 7 years or under they decrease much more slowly in the course of the disease than in adults; (2) lymphocytes do not show any deviation from those found in adults; (3) eosinophils are also the same as in adults; (4) total white count shows a leukopenia in children over 7 years, but in younger ones it occurs only in the second or even third week of the disease; (5) early examination of blood in older patients is essential in the diagnosis of typhoid fever though not as valuable as in adults, but it is as effective in prognosis.

KATO, Los Angeles.

## Chronic Infections

THERAPEUTIC ACTION OF POTASSIUM IODID IN EXPERIMENTAL SYPHILIS OF THE RABBIT. LOUISE PEARCE, Arch. Dermat. & Syph. **12**:1 (July) 1925.

Three groups of six rabbits each were inoculated. Group A received 0.006 gm. per kilogram and group B 0.0003 gm. per kilogram of potassium iodid intravenously at weekly intervals. Semiweekly injections for the first three weeks made some of the rabbits ill. Group C served as control. The observation period was four months. The dose of iodid given to Group A is stated to be comparable to that which might be given to a human being.

The average incubation period of the original testicular lesion was as follows: Group A, twenty days; Group B, twenty-three days; Group C, ten days. The orchitis in the treated developed more slowly and irregularly than in the untreated, and after development was much less severe.

The average duration of progressive activity of the orchitis was as follows: Group A, twenty-five days; Group B, nineteen days; Group C, fifty-eight days. Healing of the original lesion had taken place as follows: Group A, fifty-eight days; Group B, forty-two days; Group C, eighty-one days. The inflammatory reaction in Group B was definitely of a slighter grade than that of Group A, and the average time of healing was two weeks less.

The number of secondary lesions developing per animal was as follows: Group A, 2; Group B, 1.6; Group C, 4.1. The lesions in the treated groups were less marked and of shorter duration than those in the untreated.

The incubation of metastatic orchitis required from six to nine weeks longer in the treated than in the untreated group.

The benign nature of the infection throughout the course in the treated groups is emphasized. There was not a single instance of well marked disease in Groups A and B.

It is concluded that the drug enabled the animals to prevent the occurrence of severe manifestations to curb the progress more promptly and, in general, to exercise a more effective control over the evolution of the disease than is ordinarily the case. The therapeutic effect was evident from the beginning of the primary lesions and through the secondary period. It is suggested that the therapeutic action is associated with a stimulation or reinforcement of the host's mechanism of reaction of defense.

JEANS, Iowa City.

DISTINCTIVE CHARACTERISTICS OF INFECTIONS PRODUCED BY TREPONEMA PERTENUE IN THE RABBIT. L. PEARCE and W. H. BROWN, J. Exper. Med. **41**:673 (May) 1925.

A marked periorchitis was found to be a characteristic feature of intratesticular inoculation of rabbits with spirochetes of yaws. The lesion was of a granular or finely nodular type, with or without a diffuse involvement of the tunic, and could be recognized clinically about three weeks after inoculation, the following month showing tiny indurated nodules on the testicular covering. No lesions were discoverable in most animals three months after inoculation. These lesions were practically a constant feature and were unlike any lesion of the tunic observed after inoculation with *Spirochaeta pallida*. The organisms were disseminated to the noninoculated testicle, but no generalized lesions were observed.

THE OCCURRENCE OF STIGMATA OF CONGENITAL SYPHILIS IN RABBITS WITH SPECIAL REFERENCE TO THE FACTOR OF INHERITANCE. W. H. BROWN and L. PEARCE, J. Exper. Med. **41**:795 (June) 1925.

Rabbits born of infected parents were apparently normal at birth, but soon developed symptoms strongly suggestive of syphilis, although no infection could be demonstrated. The lesions consisted of a unilateral lesion of the cornea and iris and an abnormal growth of hair associated with an extensive alopecia affecting three of the litter of six. Three of these rabbits were susceptible to inoculation for syphilis, the other two showing negative results on examination of the popliteal lymph nodes. They are unable to say whether the stigmas presented were due to syphilis in the parents or possibly were due to some unusual circumstances of unknown origin and were of functional origin due to heredity.

JAMIESON, Detroit.

STUDIES IN EXPERIMENTAL SYPHILIS. III. FURTHER OBSERVATIONS ON THE POSSIBILITY OF CURE OF SYPHILIS IN THE RABBIT WITH ARSPHENAMIN. ALAN M. CHESNEY and JAROLD E. KEMP, J. Exper. Med. **42**:17, 1925.

In a previous paper the authors reported that syphilitic rabbits treated late in the course of the infection, when all signs of activity of the disease had disappeared, could be freed of infection, as judged from lymph node sterility, whereas, negative reinoculation tests indicated that the infection still existed.

To reconcile these results, the explanation was advanced that perhaps the failure of reinoculation was due not to a still existing infection, but to a resistance acquired as the result of the infection and which persisted after its eradication.

To obtain more information on this question, experimental syphilis in rabbits was treated with arsphenamin, early in the course of the disease in one group, and late in another group. Negative results from lymph gland

transfer indicated that cure was produced in both groups. Reinoculation resulted in reinfection (as determined by positive lymph node transfer) in twelve out of thirteen of the animals treated early, but in only one out of thirteen of those treated late in the infection.

The authors suggest that the refractory state in the second group, treated after the animals had reacted to the disease and brought about by a subsidence of the primary phenomena, may be explained by the existence of an acquired immunity which persists after the abolition of the disease, rather than to the persistence of the first infection.

The possibility that abolition of lymph node infection by treatment does not mean elimination of syphilis from the entire body has been investigated and the result reported in a subsequent paper.

STUDIES IN EXPERIMENTAL SYPHILIS. IV. THE SURVIVAL OF TREPONEMA PALLIDUM IN THE INTERNAL ORGANS OF TREATED AND UNTREATED RABBITS. ALAN M. CHESNEY and JAROLD E. KEMP, with the assistance of Allan K. Poole, J. Exper. Med. **42**:33, 1925.

Ten rabbits were inoculated with syphilis and six of these were treated with arsphenamin, beginning 181 to 194 days after inoculation. Four remained untreated. From 279 to 384 days after inoculation, the heart's blood, heart, liver, brain, mixed spleen and bone marrow, the originally inoculated testes, and popliteal lymph nodes from both groups were injected separately into testes of normal rabbits.

As determined by this method, syphilitic infection was present in the popliteal lymph nodes of all four of the untreated animals, and in many instances in one or more internal organ; whereas in the six animals treated late in the disease, at a time when refractory to a second infection, all tissue transfers were negative except in one case with a keratitis, in which injection of the involved cornea produced infection.

The authors point out that while lymph node sterility does not in every instance indicate that the animal is free of syphilis (particularly if there has been a preexisting keratitis), yet it is probably the best single index of a cure that we have.

They state that the results of this study support the idea that failure to reinoculate a treated syphilitic animal does not necessarily mean the existence of the first infection, but might be interpreted as indicating the presence of an acquired resistance which persists in rabbits in which no trace of the first infection can be demonstrated.

McCLURE, Evanston, Ill.

LESION OF INNER TABLE OF SKULL, PROBABLY DUE TO CONGENITAL SYPHILIS? IN A PATIENT WITH HEREDITARY ACHONDROPLASIA. ANDRE LERI and LINOSSIER, Bull. Soc. franç. de dermat. et syph. **31**:501, 1924.

In a mother and daughter with achondroplasia, the Wassermann reaction was negative, and there were no visible signs of syphilis. Roentgenologic studies revealed cranial lesions in the daughter.

PARKHURST, Toledo, Ohio.

SYPHILIS IN PARTURIENTS. V. MARQUES BERTRAN and J. MUNOZ, Rev. españ. de Obstet. y Gynec. **10**:201 (May) 1925.

In the 303 parturients at the Barcelona Maternity hospital, syphilis was found in sixteen. Among the syphilitic women, 23 per cent. had had abortions before

this. The fetal mortality in the untreated was 83 per cent. In all the cases of congenital syphilis in the new-born, the mothers were invariably syphilitic, but 46 per cent. were unaware of their infection. The most constant visible sign of syphilitic infection of the placenta is the discoloration. The Wassermann test was negative in 8 per cent. of the certainly syphilitic women.

[J. A. M. A.]

GERLIER'S DISEASE. KARL REHSTEINER, Schweiz. med. Wchnschr. **55**:410 (May 7) 1925.

In 1887, Gerlier reported the occurrence of a new syndrome "vertige paralysant," noted in patients of his district. The syndrome was characterized by attacks of vertigo, associated with ptosis of the eyelids and palsies of the voluntary muscles, especially those of the neck. Hatenhoff, Pégaitaz and David had also noted epidemics of this condition in the same region. In 1888, two Japanese physicians reported a similar condition in a province in Japan. With the exception of these two areas, no cases have been reported in the literature.

In 1889 Gerlier published a monograph on this subject, and named these characteristics of the condition: muscular palsies, visual disturbances and dizziness, pains in the neck and back. The palsies affected only voluntary muscles, especially extensor groups. The levator palpebrae superioris were most commonly involved. Next in frequency were the neck muscles producing a falling forward of the head on the chest (Kopfhängen). The extensors of the limbs were frequently involved and occasionally to such an extent as to produce inability to use them. The muscles of mastication and facial muscles were rarely affected. Visual disturbances and vertigo accompanied or preceded the muscular weakness. The dizziness, which might be so severe as to cause the individual to fall, was not associated with illness or loss of consciousness. The visual disturbances were usually in the nature of blurring or dimness. Diplopias were rare. No pupillary changes were noted. In a few instances a slight hyperemia of the fundi was noted.

The neck and back pains were variable, at times severe and again entirely absent. The attacks were described as usually of short duration, a single attack lasting but a few minutes. However, they might occur in rapid succession extending over several hours and representing a type of crisis.

Gerlier distinguished three types of attacks which differed from one another in intensity: (1) ptosis and mild visual disturbance (type de l'endormi), (2) ptosis and cervical weakness so that the head would fall forward, (3) dizziness, weakness of the limbs and a reeling gait.

Prodromes were rather rare, although occasionally a feeling of hunger or salivation preceded the attack. The condition would usually begin during the summer months. The attacks would gradually become more frequent, increasing in intensity so that from ten to twenty might occur in one day. There would then be a slow improvement, so that with the onset of cold weather the attacks would disappear. Attacks were noted rarely in winter. While a recurrence of the condition was uncommon, the Japanese writer reported recurrences in certain persons for a period of twenty years. In no case did death result during an attack.

Between the attacks the patients were usually quite well. Occasionally a slight ptosis or general muscular weakness would exhibit itself. In all instances, it was noted that the affection occurred in people who worked about the same barn; members of the same families who did not work about the barn were

not affected. Gerlier believed that the virus was probably produced in the manure. People working in dark, poorly ventilated barns or who had to care for the manure were affected. In northern Japan, where the barn and houses were under the same roof, all members of the family were affected. Cases have also been reported of direct transmission to nurslings through the mother's milk. In 1914 Couchoud, who studied the condition in Japan, is said to have found a staphylococcus-like organism in the human milk and in the spinal fluid of affected patients. Cultures injected into cats produced a transient picture identical with various syndromes. Gerlier had previously noted that cats, chickens, horses and other animals were affected by the disease. The spinal fluid of infected cats also showed cocci and again produced the disease in other experimental animals.

Since 1900, no cases of Gerlier's disease have been reported in Europe. In October, 1924, the author observed four cases, the patients constituting an entire family who lived together in the same house without servants. Investigation of its locality brought to light another family of four members in which all the males were affected, the mother being free. Of these seven patients, the writer examined five. In the first family (L) the father first showed signs of trouble toward the end of July, 1924. The first attacks were mild and of short duration, consisting of ptosis and blurring of vision. Later the attacks became more severe so that he could not raise the lids, and occasionally diplopia and weakness of the muscles of the neck occurred. There were no pains, and the remaining musculature was not affected except that during the attack he felt a general weakness. In the more severe attacks, dizziness was present so that walking was uncertain. About a month later the remaining members of the family were affected, the attacks varying in intensity, as in the father. The attacks rarely occurred during the early morning, but usually during the afternoon or evening, and they never occurred during sleep. With the onset of cold weather the attacks disappeared.

In the second family (Sch), about the middle of July, 1924, the father first noted that at times during his work he could not keep his eyes open and things blurred. Gradually these attacks became more severe and of longer duration. The two sons shortly complained of the same symptoms, but because of their moving away from the district could not be observed.

The examination during the interval period showed in the family L that both father and mother had a slight ptosis, and convergence was impaired in the mother and son. In the family Sch, there were no abnormal findings during this period. The father of the family Sch was observed several times during an attack. The outstanding finding was the ptosis which was so marked that with most forceful attempts the lids could not be raised. Vision was not disturbed, but convergence was entirely absent. The remaining eye movements were unimpaired. The other members were also observed in light attacks with essentially the same findings. No severe attacks were observed.

In seven patients short attacks of ptosis of the lids, convergence paralysis, weakness of the neck and mouth muscles, dizziness and visual disturbances were noted in the summer and fall of 1924. The disease appeared in the form of house epidemics. The findings presented by this group of patients is essentially like those described by Gerlier and Kubisagari. Thus far no anatomic cause has been determined for this affection. During attacks a leukocytosis was noted in several cases, which rapidly disappeared with the subsidence of the attack.

The relationship of Gerlier's syndrome to myasthenia gravis has been suggested, but there is only a superficial similarity. In myasthenia gravis the attacks are never so short. Other muscle groups are affected, and the condition does not occur in epidemics. Encephalitis has also been suggested as a possible etiologic factor, but this seems unlikely to the author. Ladame suggested that the condition was hysterical. The writer does not believe this to be true. The epidemics occurred in separated regions and in no way suggested a group hysteria.

The question of an infectious process from unhygienic conditions was investigated by the author, and while the house and barn were either adjoining or in close proximity, there was nothing to lead to the idea of marked uncleanliness.

No results were obtained by the author in inoculation tests, although cats, which appeared to be more sensitive to the affection, were not tried. Potassium iodid and solution of potassium arsenite (Fowler's solution) were used with uncertain results.

MOERSCH, Rochester, Minn.

THE RELATION OF RESIDUAL NITROGEN TO THE NITROGEN OF SERUM PROTEIN IN TUBERCULOUS PATIENTS. ISAJIRO MAEDA, J. Pediat., Tokyo, 985 (July) 1925.

In studying the chemistry of blood serum in twenty tuberculous patients, Maeda found that the serum albumin decreases remarkably but globulin increases and their relations to one another is almost the reverse of the normal condition. The total nitrogen, however, shows little or no change. The severity of disease seems to be in direct proportion to the change in the ratio between serum, albumin and globulin. In tuberculous patients the residual nitrogen, after removing proteins by other phosphoric acid, is greater in quantity than that which remains after precipitating with molybdic acid, while in the normal condition there is almost no difference in the quantity. This difference in tuberculous patients is due to the presence of the so-called albumosoid substance in large quantity. The similar findings are proved in the serum of patients with pleurisy, though to a less marked extent.

KATO, Los Angeles.

## Internal Diseases

ERYTHREDEMA POLYNEURITIS. HARRY R. FOERSTER, Arch. Dermat. & Syph. 12:17 (July) 1925.

Four cases of "acrodynia" are reported. The literature is reviewed. From the review it is concluded that the condition is of infectious origin, the toxemia producing a sensory neuritis, chiefly peripheral, with chronic inflammatory changes in the spinal cord and nerve roots.

JEANS, Iowa City.

ACRODYNIA. G. BRUTON SWEET, Arch. Pediat. **42**:543, 1925.

Acrodynia is a chronic infective disease, probably of the upper respiratory tract, the micro-organism of which has not been discovered. The onset is not infrequently acute, being attended by fever and sometimes by convulsions. In the ultraviolet rays of the mercury vapor quartz lamp we have a rapid and efficient means of cure. Five cases are reported.

VON MEYSENBUG, New Orleans.

HEMOPHILIA. EDWARD C. DAVIDSON and IRVINE MCQUARRIE, Bull. Johns Hopkins Hosp. **36**:343, 1925.

This is a careful study of the blood findings and heredity in three cases including one case of so-called sporadic hemophilia. There is also a brief review of the reliable literature.

"A typical, large, hemophilic family is described, in which fourteen proved cases of hemophilia have occurred in eight generations. Detailed reports of two of the cases representing the sixth and seventh generations are presented. Two normal female members of the same family presented no evidence of the disease, either clinically or from blood examination. The hereditary transmission occurred in this family according to the law of Nasse. No occurrence of the disease in females and no transmission through the males of the family has been observed. Of the females capable of transmitting the disease, 83.3 per cent. are known to have done so. Among the potential hemophiliacs 51.8 per cent. have proved to be bleeders.

"One typical case of sporadic hemophilia is described. The clinical picture and the blood abnormalities are identical in the sporadic type and in hereditary type of the disease.

"The blood coagulation time and the prothrombin time in the cases of hemophilia were from twice to twenty-five times as great as the normal. They both varied from time to time to a considerable degree in the case of each individual with hemophilia.

"The finding by Minot and Lee of a qualitative platelet deficiency without a diminution in the number of platelets has been confirmed.

"The bleeding time, the capillary resistance, the nature of the blood clot when finally formed, the amount of blood calcium and the number of blood platelets were at all times found to be normal in the cases of hemophilia studied.

"Blood transfusion is the most effective form of treatment for the hemorrhage in hemophilia and should be employed as a prophylactic measure preceding surgical operations."

PYLORIC STENOSIS OF INFANTS. WILBURT C. DAVISON, Bull. Johns Hopkins Hosp. **37**:75, 1925.

This is a statistical analysis of sixty cases of pyloric stenosis, all the patients admitted to Harriet Lane Home from October 1913 to June 1922. A discussion of medical and surgical treatment of this condition is to appear in later papers.

The cases are in two groups, those treated medically and those treated surgically. The various factors in relation to pyloric stenosis, as symptoms and signs, type of onset, birth order, color and sex, birth weight, loss or gain in weight, seasonal variation, etc., are all taken up in detail and tabulated.

The case fatality rate was highest among those who were not constipated, whose onset was sudden, who weighed less than 7 pounds at birth and on admission, and who had lost the most weight since birth. There were no fatalities in infants overweight at birth or who had gained in weight between birth and admission to hospital.

Davison is unwilling to draw definite conclusions from so small a series but thinks the following deductions are possible.

1. To operate on all patients who are in such bad condition on admission to the hospital that delay would be fatal.

2. To make a trial of medical therapy in infants who are not in a critical condition.

3. To operate on patients in whom medical therapy is not producing any improvement.

By selective therapy, rather than by exclusively surgical or medical treatment, the total case fatality rate can be reduced.

LYTTLE, New York.

EXPERIMENTS ON CANCER PRODUCING SUBSTANCES. E. L. KENNAWAY, Brit. M. J. **2**:1 (July 4) 1925.

Further experiments on the formation by heat of cancer producing materials are described by Kennaway. The nine products tested were obtained from the following sources at, approximately, the temperatures stated: acetylene (700, 800 and 900 C.); California petroleum (880 C.); isoprene (700 C.); Durham Holmside coal (450, 560 and 1,250 C.); human skin (290 C.); yeast (290 C.). It is stated that the pyrogenous materials derived from acetylene, isoprene, petroleum, yeast and skin produce cancer simply because they are all "irritants"; and that the multiplication in the laboratory of instances of "chronic irritation" is not required. To apply this to a substance, after it has been shown to produce cancer, the term "irritant" gives an appearance of explanation which is illusory. There seems to be a tendency at present to state that a substance such as soot gives rise to a cancer because it is an irritant, and at the same time tacitly to regard it simply as an irritant because it gives rise to cancer; this circular treatment of the matter is of no value at all. The irritation which causes the growth of cancer must be a special kind or must act on some special element in the tissues. No invariable relation has been found between the temperatures at which these various materials are formed and their comparative activity in producing tumors. Thus the three tars made from coal at 450 C., 560 C. and 1,250 C. show an ascending order of potency; the 820 C. isoprene tar is more active than the 700 C. tar; and experiments still in progress indicate that the 920 C. tar will prove more effectual than the 780 C. tar. In all these cases the higher temperature gives the more active product. But, on the other hand, in the case of acetylene, a low temperature (700 C.) gives a product more active than that produced at from 800 to 900 C. The idea suggests itself that acetylene may be a decomposition product common to coal, mineral oils, yeast, skin and isoprene, and that the cancer producing material obtained from these very diverse sources is actually formed from acetylene by the synthetic process discovered by Berthelot. Probably the yield of cancer producing substance depends largely on catalytic reactions which cannot as yet be controlled.

[J. A. M. A.]

FIBROSIS OF BRONCHI AND LUNGS IN CHILDHOOD FOLLOWING BRONCHOPNEUMONIA. C. MCNEIL, Edinburgh M. J. **32**:152 (July) 1925.

The author gives eighteen case abstracts of fibrosis of the pulmonary tract in childhood. A number of confusing terms have been used by different writers. Bronchiectasis as described by Laennec is the one most used at the present time, but McNeil favors fibrosis as the most accurate. The principal clinical features are the peculiar convulsive cough following acute pulmonary inflammation and lasting till adult life; recurrences of cough and pneumonia are easily induced; recurrences of lung consolidation; the heart pushed to the affected side; cyanosis and clubbing of the fingers and toes are common but

not always present; the weight and nutrition are not much impaired, and the cough is worse on waking in the morning.

The fibrosis is unilateral, the chest flattened on the affected side with poor expansion. Dulness is usually present, due to the fibrosis of the lung and pleural surface. Breathing is bronchial with rhonchi or crepitant râles. An associated bronchitis is rather confusing in determining the physical signs.

The roentgenogram of the chest accords with the clinical examination. There is a fine shadowing with an increase in the hilum shadows in the group of cases showing incomplete fibrosis, a picture which does not differ from chronic bronchitis. In complete fibrosis, the shadow is dense and extensive on the affected side, involving most of the lung, with the trachea displaced toward the fibrotic side.

In most of these cases the morbid anatomy reveals bronchiectasis which is borne out by the clinical evidence of copious expectoration, cyanosis and plugging of the sphincters. Paroxysmal cough and cavernous breathing are not sufficient for the diagnosis of bronchiectasis.

The diaphragm is also displaced upward.

In spite of the older literature, this fibrosis is not tuberculous. McNeil does not believe that these children are peculiarly apt to develop tuberculosis. This is borne out by the scarcity of tuberculin reactions, nor is this disease connected with the fibrosis of syphilis. Two fairly extensive series of cases showed practically no syphilitic reactions or clinical stigmas.

McNeil describes the less complete type which has a history of long-standing paroxysmal night cough following an early attack of bronchopneumonia, but without definite physical signs of fibrosis or confirmation by the roentgen ray. Such cases are numerous and probably make up a considerable number of the cases in which the roentgenogram cannot be easily interpreted.

For the pathology and anatomy one is referred to Laennec's description of the lungs in his four cases. The microscopic anatomy shows the infiltration of the lung connective tissue by organized fibrous tissue, especially in the peribronchial, interalveolar and subpleural regions.

Such children not only live, but they survive through adult life and even old age, being able to work. The cough and physical signs of consolidation may become markedly less as the child grows older. The cicatrized and fibrotic lung is little changed by treatment and is not of much danger to the patient. The catarrhal condition and cough are benefited by complete rest, warm covering, fresh air and sunshine. Inversion of the child or postural coughing is of benefit when there is marked bronchiectasis. Vaccines are without result. Relapses are apt to occur persistently and without much benefit from treatment.

CASES OF CONGENITAL CARDIAC DEFECT IN CHILDREN. AGNES R. MACGREGOR, Edinburgh M. J. **32**:251 (May), ibid., 370 (July) 1925.

The first case in the series reported by MacGregor was reported in the *Edinburgh M. J.*, February, 1925, and abstracted in a previous number of this Journal.

In the May number the author reports the case of a child, aged 7 weeks, with rare cardiac abnormalities, namely, the absence of the right auriculo-ventricular orifice and defects in the septum between the auricles and also between the ventricles. No murmur was present and heart disease was not suspected. However there had been cyanosis and coldness of the extremities and a gasping respiration with high temperature just before death. It is

interesting to know that there is a record of a person who lived to the age of 21 years, with the absence of an opening between the right auricle and ventricle. The writer discusses the anatomy and the circulatory changes in such defects.

In the July number, the author reports a markedly cyanosed baby dying at 4 days of age. The heart was somewhat enlarged due to the increase in the right ventricle. A single large artery arose from the right ventricle in the position of the pulmonary artery, but its caliber was small which restricted the supply of blood to the lungs. There was no aorta arising from the left ventricle. The stem of the vessel from the right ventricle gave off the pulmonary artery and then continued as the aorta. There was no ductus arteriosus. The deformities were due to a failure of development in the aortic septum which normally divides the arterial trunk into an aortic and a pulmonary portion. The ventricular septum is always defective in these cases, there being a free communication between the two sides of the heart. This case is not so rare as the first two in the series.

NEFF, Kansas City, Mo.

SOME FACTORS OF SIGNIFICANCE IN ADOLESCENT GOITER. H. GARDINER-HILL, R. C. BRETT and J. FORREST-SMITH, Quart. J. Med. **18**:133, 1924-1925.

The authors have studied 100 cases of goiter in adolescents between the ages of 10 and 20. Using Marine's classification they have divided their cases into colloid goiter, of which there were seventy-nine cases; exophthalmic goiter, of which there were sixteen cases; adenomas and endemic goiter of which there were three and two cases respectively, too few to use as a basis for conclusions in this work. In the group of patients with colloid goiter the majority were above the average height for their age; in weight, those with hyperfunction were below and those with hypofunction above the average. Menstruation in those with hyperfunction and in those with exophthalmic goiter tended to be irregular, scanty or absent; in those with hypofunction it tended to be excessive. The values for basal metabolism in general agreed with the clinical grouping. Blood sugar curves after injection of 50 gm. of glucose showed a delay in the return to normal in cases of both hyperfunction and hypofunction. Unfortunately, the authors have not stated the criteria they have used in the classification of their cases, which is of necessity clinical and not, as they suggest at the outset, pathologic. Moreover, they have not included the age incidence of their various groups.

JOSEPHS, Baltimore.

SPLENECTOMY FOR HEMORRHAGIC PURPURA. A. CHAUFFARD and P. DUVAL, Presse méd. **33**:961 (July 18) 1925.

The case observed by Chauffard and Duval, in a young girl, was characterized by a long bleeding time, variable from twenty or thirty minutes to two hours, and by a decrease of the blood platelets. Examination of the patient ten weeks after the spleen had been removed showed apparently complete clinical recovery, and a normal condition of the blood. The sclerotic spleen, which destroys the red corpuscles in hemolytic jaundice, may affect the platelets in hemorrhagic purpura.

[J. A. M. A.]

ACUTE POLYARTICULAR RHEUMATISM IN THE NURSLING. MAMERTO ACUÑA, Arch. Am. de med. **1**:49, 1925.

The author reports four cases of acute articular rheumatism occurring in young infants, ranging in age from 7 to 20 months.

The small joints in the hands, feet, fingers and toes, were principally involved. The parts are generally quite swollen and may show edema. There is generally no involvement of the heart even though there are repeated exacerbations of an attack.

Large doses of the salicylates can be given the young infant without any ill consequence.

SCHLUTZ, Minneapolis.

## Nervous Diseases

NEGATIVISM IN CHILDHOOD. JOSEPH H. MARCUS, Arch. Pediat. **42**:455, 1925.

Training the infant in regular habits is essential to a happy adaptibility in childhood and adolescence. Displaying an attitude of stubbornness more forcible and lasting than the child's will eliminate many negative traits. Two histories are essential: a medical and an environmental history. The child should be observed within the confines of his own home. Healthy inattention is an excellent form of medication.

THE NERVOUS CHILD. ALFRED GORDON, Arch. Pediat. **42**:472, 1925.

The special characteristic features of the nervous child, namely, the power of imitation, the influence of the environment and of the milieu, the suggestibility, the tendency of becoming readily influenced, the nefarious influence of obnoxious scenes and of reading undesirable literature, all lead directly to the problem of prophylaxis, which is fundamentally based on avoidance or removal of all agencies that are capable of accentuating these characteristics. The "nervous child" is a problem of social value, since the instances of delinquency and criminality of adolescents are gathered among that class of individuals. It is not sufficient to endeavor to ameliorate the morbid tendencies, but what is better yet is to prevent the procreation of such persons.

MONGOLIAN IMBECILITY AS AN ANTHROPOLOGIC PROBLEM. CHARLES HERRMAN, Arch. Pediat. **42**:523, 1925.

Recessive unit factors may reappear in a descendant, after remaining latent or concealed for many generations. Defective embryos are the least likely to mature, probably due to the presence of so-called lethal factors which cause disintegration of the fertilized ovum. Other congenital anomalies are often present in mongolian imbeciles. Many of these are definitely known to be due to the presence of recessive unit factors. There is probably an infusion of mongolian blood in a certain percentage of Europeans. There are many points of resemblance between mongolian imbeciles and racial mongols. There are several points of resemblance between mongolian imbeciles and anthropoid apes, but there does not appear to be conclusive evidence that they are more closely related to the orang than to the other anthropoids. Both the anthropoid and the mongolian unit factors must have been present in the parent trunk from which the human and the anthropoid branches were derived. If we assume that mongolian imbecility represents a reversion to a primitive type, we have an explanation of the presence of certain anthropoid and certain mongolian characteristics, for it is not surprising that occasionally a descendant should exhibit a combination of these unit factors.

VON MEYSENBUG, New Orleans.

A Comparison of the Concentrations of Inorganic Substances in Serum and Spinal Fluid. Bengt Hamilton, J. Biol. Chem. **65**:101, 1925.

Determinations were made of the inorganic constituents of blood serum and spinal fluid of epileptic patients, blood and spinal fluid being withdrawn at essentially the same time. The author feels he is justified in concluding that in seventeen cases of epilepsy, a comparison between the serum and spinal fluid in respect to organic constituents gave an entirely negative result as to pathologic findings.

The author discusses the relation between the inorganic constituents of blood and spinal fluid.

Higgins, Cincinnati.

The Histology of Juvenile Amaurotic Idiocy. J. G. Greenfield and Gordon Holmes, Brain **48**:183, 1925.

Two cases are described, clinically, which occurred in the same generation in a family in which the parents came of pure English stock. Both boys were normal and in good health until 9 years of age, when gradual failing of vision was noticed, followed later by epileptiform convulsions, mental deterioration and finally blindness and paralysis. Examination of the fundi revealed extensive macular and perimacular atrophy of the retinas. In these areas the retinas were grayish and had fine granular pigmentary deposits in them, while the optic disks revealed few or no changes. In the patient dying at the age of 15, a complete histologic examination was made. There were no changes worthy of note in the internal organs or glands of internal secretion, except the suprarenals, in which there was intense fatty infiltration of the cells of the deeper layers of the cortex. The most striking gross abnormality in the brain was the small size and firmness of the cerebellum, which was about half its usual bulk, with marked sulci between the various lobes. Histologically the meninges and blood vessels were normal. The primary pathology was that of neuronic degeneration. The cells from all parts of the brain and cord were pear shaped, with a normal amount of Nissl granules toward the apical dendrite, the basal portion of the cell being distended with a granular lipoid substance to about twice its normal diameter. In some cells, as in the nuclei pontis, and the olivary and dentate nuclei, the change was more pronounced; the cells seemed to be completely filled with lipoid granules and to have lost all their Nissl bodies. In the cerebellum the actual changes in the nerve cells, and especially the Purkinje elements, were similar in nature to those affecting the cells of the rest of the nervous system, differing from them only in severity. At the base and along the course of the dendrites, rounded swellings filled with lipoid were frequently seen. The striking features were the complete absence of all cells of the granular layer, the diminution in number of the Purkinje cells, and the loss of basket fibers surrounding those cells of Purkinje which persisted, combined with a considerable increase of neuroglia in the position of the granular layer. The white matter of the cerebellum, as that of the cerebrum, was little affected, except for the frontopontile bundle. The most striking feature in the histologic changes in the retina was the degeneration of its outer layers, which was mild at the periphery and intense toward the macula. The earliest recognizable lesion was a breaking up of the rods and cones associated with a rarefaction and narrowing of the outer nuclear layer. The next stage was the replacement of the degenerated external layers of the retina by proliferating neuroglia, followed by a proliferation of the pigment epithelial cells and invasion of the degenerating retinal layers by them. The

inner layers of the retina remained practically intact, except that the nerve cells of the ganglion layer were affected similarly to the cells of the central nervous system.

The authors reviewed the previous work done on this disease, as well as the findings in the infantile form, and advance the argument that the infantile and the juvenile types of amaurotic idiocy are manifestations of the same pathologic process, the histologic differences being mainly dependent on the mode of reaction of the nervous tissues and the incidence of the disease in special structures.

STACK, Milwaukee.

SO-CALLED PARKINSONIAN SYNDROME AND ENCEPHALITIS. EDWIN BRAMWELL, Edinburgh M. J. **32**:129 (June) 1925.

Bramwell discusses the essential features of the syndrome and its mode of production. The discussion is mostly from an anatomic standpoint and has no application to therapy.

A CASE OF NEUROBLASTOMA (NEUROCYTOMA). R. A. FLEMING and JAMES DAVIDSON, Edinburgh M. J. **32**:142 (July) 1925.

The case is reported of a boy, aged 4 years, who fell out of bed, landing on his head; two days later he became a little deaf and the mother noticed large veins on the forehead and sides of the head. One week later the boy appeared sick, with pallor, discolored eyelids, intermittent headaches every two or three hours, vomiting, increase in size of the head. About two months later he became blind suddenly, the eyes being prominent. The blood showed the picture of pernicious anemia. His memory and intelligence were normal. He died four months after the injury.

The necropsy findings are given in detail, the characteristic of the head findings was a fleshy-like tumor replacing all of the subcutaneous tissue of the scalp, penetrating the skull into the extradural space. The orbits had become involved externally enucleating the eyeballs. The growth did not become subdural in any place, the brain remaining free. One suprarenal gland was affected, and there was also a metastatic growth in the pancreas. The long bones were invaded.

Such a tumor was originally classed with the sarcomas, but now it is recognized that new growths of the nervous system are composed of the developing cells in the various parts of the nervous system. Hutchison once published a record of ten cases in children, in which he concluded that the primary growth (which he called sarcoma) occurred in the suprarenal with metastases in the cranium. In all cases an injury was noted previously and there were ecchymoses of the eyelids. Secondary anemia and a rapid course occurred in all cases. This group of symptoms was constant enough to be regarded as a syndrome.

The histologic examination corresponds to the tumor structure of neuroblastoma.

THE TREATMENT OF SPASTIC PARALYSIS BY SYMPATHETIC RAMISECTION. W. Q. WOOD, Edinburgh M. J. **32**:305 (June) 1925.

This is a short review of the anatomy and surgery of spastic paralysis, largely discussing the joint work of the Australians, Hunter and Royle, who were in America in 1924. Improvement in muscular control is the important result of plastic work of this kind, but as Royle states no method of treatment can be effective unless there is definite cerebral control.

NEFF, Kansas City, Mo.

SUCCESSFUL RESEARCHES IN THE TREATMENT OF INFANTILE PARALYSIS. G. MURRAY LEVICK, Lancet **2**:323 (Aug. 15) 1925.

The following measures were adopted by this author:

1. General radiation of the skin by artificial sunlight (as the real sunlight was so seldom available).

2. Local treatment of the affected muscles by rays from long ray lamps passed through red filters.

3. Electrical treatment.

4. Reeducation of voluntary stimulus.

5. Instrumental support for the paralyzed muscles and then (most important) abandonment of support, in some cases at an early stage. The writer calls particular attention to this matter.

6. Massage.

The cases selected for treatment were children, some of whose muscles gave no response to the interrupted galvanic current. Moreover, the acute attack resulting in the degeneration of the nerve fibers had taken place so many years before that, acting on experience gained from the practice of massage and electrical treatment alone, one would have said that further measures with a view to restoring function of the paralyzed part would hardly be justified. At the same time palpation gave the impression that the muscles had not completely atrophied.

The writer feels that the treatment by light stands out as a great advance, as in his wide experience with the treatment of cases of infantile paralysis he has never obtained results that can compare with those that have been obtained since instituting the general and local treatment by light.

LANGMANN, New York.

LANDRY'S PARALYSIS WITH FINDINGS OF ACUTE ANTERIOR POLIOMYELITIS. MONA ADOLF, Jahrb. f. Psychiat. u. Neurol. **43**:40, 1924.

CASE 1.—A previously healthy man suddenly became ill with pains and weakness in one leg; the next day both legs became paralyzed. Within a few hours after admission to the hospital, the paralysis rapidly ascended to the trunk and upper extremities; simultaneously with the progression of the paralysis he developed severe dyspnea, to which he succumbed. On histologic examination the brain and cord showed marked involvement of the vessels; the perivascular lesions and the intense destruction of the ganglion cells with the existing neuronophagia were identical with the histologic picture usually observed in poliomyelitis. Bacteriologic examination was negative. As careful investigation revealed no relationship (I presume the author means, no *etiologic* relationship) to infantile spinal paralysis, the case was diagnosed as acute anterior poliomyelitis adultorum with a Landry syndrome.

CASE 2.—A man, aged 24, became ill on Nov. 23, 1919, with general prostration and drawing pains in the joints. After staying in bed for a few hours he found that he was unable to move both lower extremities; there were no objective sensory disturbances. On the following day he was unable to sit up in bed, and his neck became rigid. On November 25, he was hardly able to move his upper extremities; his sphincters remained intact. On November 26, he developed severe dyspnea, for which he was removed to the hospital. Examination showed normal cranial nerves (in view of the reported dyspnea, I doubt the correctness of this observation), absent reflexes (not mentioned

whether deep, or superficial, or both); no Babinski sign, positive Kernig sign; slight movement of the upper extremities, complete paralysis of the lower, except for slight ability to move the toes; there were no sensory and no sphincteric disturbances. The patient was extremely pale; his lips and nose were cyanotic. (There is no report of spinal fluid findings in this case nor in Case 1.) The weakness and paralysis were steadily increasing, and death occurred on Nov. 30, 1919. Necropsy showed evidences of a hemorrhagic encephalitis and myelitis. Sections of almost all levels of the cord and brain stem showed the histologic picture of poliomyelitis. The meningeal infiltration and hyperemia were much more extensive than in Case 1; there were many hemorrhages throughout the cord, especially in the lumbar enlargement, and marked destruction of ganglion cells. In the region of the aqueduct of Sylvius there were many distended capillaries and small-cell, perivascular infiltrations, but no such hemorrhages as are usually found in Wernicke's superior hemorrhagic encephalitis. The cord also showed glial changes. The differences in the histologic pictures in the two cases is attributed by the author to the differences in the duration of the illness, the latter being much longer in Case 2 than in Case 1.

KESCHNER, New York.

THE MYOCLONIC FORM OF ENCEPHALITIS. WERNER REIMOLD, Ztschr. f. d. ges. Neurol. u. Psychiat. **95**:21 (March) 1925.

The question of myoclonus has been an open one since Friedreich's contribution on paramyoclonus multiplex in 1881, and since Unverricht reported on the familial type of myoclonus. Encephalitis has of late years again directed attention to this problem. Mann reported eighty cases of encephalitis in the epidemic of 1922-1923, in 38 per cent. of which there was myoclonus either in pure form or in combination with paralysis agitans, chorea or athetosis. The occurrence of myoclonus was particularly frequent in the epidemic, while paralysis agitans was not common. A review of the findings since the first publication of Economo in Vienna and of the French in 1915-1916 shows that lethargy was the outstanding feature of the first epidemic, while in the succeeding epidemics postencephalitis disturbances became more prevalent, especially parkinsonism. Myoclonus was at first infrequent, but gradually increased in incidence until in 1919-1920 it was frequent. Grünewald reports an incidence of myoclonus in 32 per cent. of encephalitic patients up to 1922-1923. Wechsler found that a combination of psychic symptoms and myoclonic twitchings characterized the last New York epidemic. Crispel found myoclonic twitchings in twenty-three of forty-two patients from January to March, 1923. Hunt found "hyperkinetic symptoms" frequent during the same period. Smith, in an epidemic in the Philippines from November, 1922, to early in 1923, observed a predominance of hyperkinetic, myoclonic symptoms.

The Breslau epidemic, which the author reports, reached its peak simultaneously with that of the grip, which was toxic in nature. The disease came on either slowly with uncertain feelings of malaise, with headaches over a long period, later on vertigo, vomiting and fever, with the final onset of clonus after days or weeks; or its onset was acute, with severe pains in the muscles, which after a short time showed twitchings. In some cases the onset was subacute, with psychic disturbances, delirium, confusion, high fever and sooner or later, myoclonus.

The muscles most frequently involved in myoclonus are the adductors of the upper arm (pectoralis major), the flexors of the forearm (biceps, brachialis and brachioradialis), together with the superficial and deep flexors of the

wrist, and the interossei. The combined contraction of these muscles produces a characteristic rhythmic clonus with powerful adduction of the upper arm and flexion and pronation of the forearm. Through simultaneous contraction of the interossei a picture is produced almost similar to that seen in parkinsonism. Synchronously one often finds clonus of the respiratory muscles, which Stern has described under the term polypnea. The diaphragm, intercostals and subsidiary muscles are involved, and contract from fifty to seventy times a minute independent of and uninfluenced by volition. Elevators of the shoulder girdle may be likewise affected, e. g., the trapezius, levator scapulae, rhomboids, etc., contraction of which produces elevation of the shoulder. The muscles of the lower extremity are less commonly involved. Of the muscles of mastication, the masseters and temporals are most frequently affected, at times also the pterygoids. In the neck, the sternomastoids are most often affected. Clonus of the abdominal muscles was infrequently seen. Particular attention is called to the combination of myoclonus with fibrillary twitchings (myokymia).

ALPERS, Philadelphia.

CASE OF AMYOTROPHIC LATERAL SCLEROSIS IN A CHILD. JUN TAKAYA, J. Pediat. Tokyo, p. 669 (May) 1925.

The child reported was 9 years and 11 months of age. The family history was negative except there was insanity in a member of the maternal family. The past history was negative. The main complaint at time of examination was that about ten months ago, the child began to experience some difficulty in holding a fork on eating. About four months later, salivation and nasal discharge appeared and difficulty in motion especially of hand and fingers was noted. The voice became somewhat hoarse and the child had a tonsillectomy operation which only slightly improved the condition. The child tired easily on effort and on reading the enunciation became indistinct. Two months later, the boy began to have difficulty in walking and the swallowing act became also abnormally difficult. Examination revealed a somewhat undernourished child with pale yellow skin. The expression of the face was dull, though not parkinsonian. The child climbed up on his knees when getting up from a lying position. On walking, the feet described semicircles. There was a slight asymmetry of two sides of the face, but the eyes, nostrils and oral outlines were all normal. The eyeground showed no abnormality. The tongue could not be protruded straight. The right clavicle was higher than the left. The upper and lower extremities were stiff. The lungs and heart were negative. The abdomen was slightly distended. The liver was not palpable but the spleen was slightly enlarged. All reflexes were somewhat exaggerated. The urine and stool examination were negative. Blood examination showed 4,176,000 red blood cells, 4,200 white blood cells, hemoglobin 93 per cent., and color index 1.1. The differential count showed 69 per cent. polymorphonuclears, 24 per cent. small lymphocytes, 4 per cent. eosinophils, 1.2 per cent. transitionals, 0.4 per cent. basophils and 0.8 per cent. large lymphocytes. The spinal fluid had a pressure of 180 at the beginning and 120 at the end, and contained one cell per 1 cm.; the Haynes reaction was slightly positive and there was also a trace of globulin. From the foregoing findings, the author concludes that the case belonged to the type of Carrell-Strümpel.

Glioma of the Central Nervous System. Tokutaro Nagaoka, J. Pediat., Tokyo, p. 803 (June) 1925.

A review of the literature shows that a glioma usually occurs on the retina and rarely at any other place in the central nervous system. Nagaoka reports four cases of glioma of the central nervous system. Of the four, three were seen in males, all children and young adults. There were no developmental or congenital defects in these patients. In two cases the tumor was located in the cerebellum, in one the spinal cord and in the fourth the pons and the stem were affected. Microscopically, the glioma cells showed little tendency to infiltrate the surrounding tissues, the growth taking place by the increase of glioma cells themselves from the point of origin. Morphologically, there is no resemblance of the glioma cells to epithelial cells.

Kato, Los Angeles.

## Diseases of the Ear, Nose and Throat

Acute Ethmoiditis with Rupture Into the Orbit. Arthur C. Jones, Ann. Otol., Rhinol. & Laryngol. **34**:860-868 (Sept.) 1925.

The author reports three cases of orbital abscess secondary to acute ethmoiditis, and he feels that the following points are of extreme importance as factors in producing the dangerous condition of ethmoiditis with rupture into the orbit.

1. The youth of the patient and the probable lack of a firm, bony development.

2. The swelling of the mucosa of the ethmoid allowing the bacteria present to grow under anerobic conditions.

This anerobic condition causes tremendous pressure of the pus. This pressure is due to the carbonic acid which is formed by the organisms. The gas being unable to diffuse or pass out into the surrounding tissue, causes the increase in pressure.

The author believes that the fulminating character of acute ethmoiditis which breaks through into the orbit is due to a chemical action produced by the bacterial growth which leads to the formation of carbon dioxid under great pressure, and that the etiology is not always a defect in the osseous boundaries.

H. H. Vail, Cincinnati.

Lateral Sinus Thrombosis Without Elevation of Temperature. J. W. Holderman, Arch. Otolaryngol. **1**:488 (May) 1925.

The author has collected thirty-one cases from the literature, including his own. Low virulence of infection, an obliterating thrombus, an aseptic thrombus or a fistula in the sinus with drainage through the mastoid cavity may account for the lack of the usual temperature curve. The reports show an equal distribution of afebrile lateral sinus thrombosis as a complication of acute and chronic middle ear disease. Fourteen patients had sinus abscess; the remainder had firm or totally organized thrombi; eleven had headache. In most instances, if we find a thrombus completely organized and no temperature disturbance, ligation on the jugular vein and removal of the clot is not necessary.

Tests of Hearing of Five Hundred Average Ears by the Audiometer. Dana W. Drury, Arch. Otolaryngol. **1**:524 (May) 1925.

Five hundred normal persons were tested with the audiometer in order to standardize the technic. Half of the subjects were males. The average age was

about 18 years. They were divided into ten equal groups as follows: medical students, nurses, trained and untrained telephone operators, public and private school children, blind children, college and music students. The blind children do not hear more accurately than normal children, but their coordination is quicker. Children in an outdoor private school made a better record than those in a state school. The glee club, trained telephone operators and athletes made high records, showing the effect of training and of good health on aural acuity. High notes are apparently more readily perceived than low notes. The upper limit of hearing varied considerably.

HUNTER, Philadelphia.

STAMMERING AND STUTTERING FROM THE MEDICAL VIEWPOINT. MAY K. SCRIPTURE and JOHN A. GLASSBERG, Arch. Pediat. **42**:513, 1925.

The treatment of speech disorders is primarily a medical problem and then an educational one. The best form of therapy is that under a medical speech specialist well versed in neuropsychiatry, psychology, rhinolaryngology and phonetics. Many behavioristic attitudes are caused by speech disorders. Among them are mental retardation, feeblemindedness, inferiority complexes, shut-in personalities, shyness, timidity, maladjustment, suicidal tendencies, emotional instability, criminality and other antisocial characteristics. Stuttering and stammering are distinct speech disorders. The former is difficult speech and the latter incorrect speech or mispronunciation. The cause of stuttering is subject to much controversy. We find it to be an underlying neuropathic predisposition and exciting cause which is in the nature of a nervous shock. Stammering for the most part is a speech disorder, due to a rhinolaryngologic defect, which may be adenoids, abnormal length and thickness of the uvula, abnormal size and tumors of the tongue, hematrophy of the tongue, cleft palate, hare lip, deformities of the jaws, improper development of the palatal arch, intranasal obstruction, tongue tie or defective hearing. The treatment in every case of stammering is, first, removal of the rhinolaryngologic abnormality and then proper breathing exercises, correction of the bad speech habits and phonetic reeducation.

VON MEYSENBUG, New Orleans.

MASTOIDITIS, A CAUSE OF GASTRO-INTESTINAL DISTURBANCES IN INFANTS. H. W. LYMAN, J. Missouri State M. A. **22**:293, 1925.

A close relationship exists in infants between a middle ear infection and disturbances of the gastro-intestinal tract. In these cases there are inflammatory conditions of the middle ear, temperature of from 38 to 40 C., vomiting, diarrhea and loss of weight; the latter conditions are not relieved unless the infection in the ear is relieved. Some cases, however, go to a fatal termination, even though the drums are opened and drainage maintained. These latter bad results Lyman ascribes to systemic absorption of toxic materials, the drainage through the drum head not being adequate. Inadequate drainage, he explains by the persistence of the convolutions in the epitympanic space. To relieve this infection, a simple mastoid operation is done under local anesthesia, with good results.

Lyman emphasizes the fact that the ear symptoms are not such as to point to mastoid abscess but that the mastoid operation is done to relieve the continued digestive disturbances with fever.

SCHORER, Kansas City, Mo.

CONTRIBUTION TO THE PATHOLOGIC ANATOMY AND PATHOGENESIS OF DEAFMUTISM. III. BILATERAL COMPLETE DESTRUCTION OF THE MEMBRANOUS AND OSSEOUS LABYRINTH, WITH SPONTANEOUS HEALING, AS A CAUSE OF DEAFMUTISM. O. STEURER, Ztschr. f. Hals-, Nasen-u. Ohrenh. **11**:339, 1925.

The changes found in temporal bones of deafmutes do not differ generally in kind from residues of inflammations in nondeafmutes. Yet there are some peculiarities concerning the genesis, because labyrinth changes in deafmutes are bilateral. In later life unilateral inflammations of the labyrinth are caused by an acute or a chronic middle ear suppuration, especially a cholеastomatous suppuration, the inflammation of the labyrinth which develops in early youth bilaterally is more frequently the result of a specific or nonspecific meningitis. A smaller number of the inflammations of the labyrinth in early youth can also develop after necrotizing middle ear inflammations in scarlet fever and measles. The more pronounced changes may be localized in the membranes of the windows and in the semicircular canals in tympanogenic labyrinthitis, and in the aquæductus cochlearis and the cochlear nerve in meningogenic labyrinthitis. The pathologic anatomic changes caused by inflammatory processes in the labyrinth are especially known by the comprehensive studies of Friedrich, Goerke, Hinsberg, Manasse, Uffenorde and Zange. As the final stage of the lightest form of labyrinth inflammation, of serous labyrinthitis (labyrinth hydrops) degenerative changes of the epithelial covering of the endolymphatic spaces can be seen, especially atrophy of the stria vascularis and of Cortis organ. The latter may disappear entirely. These changes may frequently be connected with an enclosing growth of epithelium, with changes of the form and position of Corti's membrane and dilatation of Reissner's membrane (posthydropic degeneration of the neuro-epithelium [Wittmaack]). Such changes have been described previously by Steurer. In the serous-fibrinous and in the lighter form of suppurative inflammation of the labyrinth, the exudate is changed into connective and finally into osseous tissue. In the final stages of this form of inflammation the perilymphatic spaces are filled, partly or completely, with more or less compact masses of connective tissue or bone (connective tissue or osseous obliteration of the labyrinth [Wittmaack]). In these cases the endolymphatic spaces show mostly degenerative changes described before as posthydropic degeneration of the neuro-epithelium. Findings of this nature in temporal bones of deafmutes have been described in great numbers, among others by von Stein, Denker, Alexander and Neumann, Linck and Uffenorde. The grave forms of suppurative labyrinthitis and the necrotizing inflammations of the labyrinth which lead to a suppuration respectively necrotizing destruction of the soft parts of the labyrinth and frequently to lesion and destruction of the adjoining osseous capsule of the labyrinth, heal in the following manner. The whole inner ear is changed into a uniform firm mass of connective or osseous tissue. In contradistinction to the osseous obliteration of the labyrinth after fibrinous inflammation, the former cannot be discriminated against the surrounding old osseous structure of the labyrinthian capsule (according to Wittmaack, labyrinth destruction ending in phthisis of the labyrinth). Steurer describes such a case in full. The patient, a woman, aged 48, a deafmute, died of insufficiency of the heart. No particulars concerning the development of the deafmutism and previous diseases could be obtained. Steurer examined the temporal bone microscopically and could establish the fact that deafmutism resulted from bilateral destruction of the whole labyrinth with spontaneous cure by new formation of connective tissue and bone. With the exception of a similar but not quite so pronounced case described by Schwartze, Steurer does not know of a case of deafmutism,

in the literature, with such pronounced changes of the inner ear. A peculiar change is mentioned by Steurer in the right temporal bone of the patient. In the right vestibule numerous nerve fiber bundles could be recognized crossing one another irregularly. They are newly formed fibers. Schwartze, Schwabach, Lange, Mayer, Zange, Brock and Preuss have described similar findings. Marx observed a new formation of nerve fibers in a pigeon after experimental destruction of the labyrinth. Where all the authors could show that the proliferating nerve fibers emanated from rests of the vestibular nerve, the arrangement of the newly formed nerve bundles in Steurer's case points to the fact that they originated partly also from the descending branch of the facial nerve.

AMBERG, Detroit.

## Diseases of the Skin

THE MOTHER'S MILK AS A SOURCE OF INFECTION IN EPIDEMIC PEMPHIGUS NEONATORUM (IMPETIGO CONTAGIOSO BULLOSA). R. R. MELLON, D. CALDWELL and W. W. WINANS, Am. J. M. Sc. **169**:419 (March) 1925.

Four of six outbreaks of pemphigus neonatorum occurring during a three year period were found to be due to the presence of *Staphylococcus aureus* in the mothers' milk: one was due to an infected burn; the origin of one was undiscovered. In a sporadic case, the mother had had an erythematous eruption resembling a drug rash. Cultures were later taken from the milk, using both the first and the last pumping, and it was found to contain pure cultures of *Staphylococcus aureus* and *albus* with attendant hemolysis. The lesions on the baby cleared as soon as the child was taken from the mother's milk. Similar findings were reported in later outbreaks; in one instance two babies of different mothers taking the same milk developed the lesions simultaneously. The mothers who have the staphylococcus in the milk are regarded as carriers.

PRIMARY INOCULATION TUBERCULOSIS OF THE SKIN WITH METASTASIS TO REGIONAL LYMPH NODES. J. H. STOKES, Am. J. M. Sc. **169**:722 (May) 1925.

With a review of the literature, Stokes gives a report of ten cases of primary skin tuberculosis inoculation, and emphasizes the importance of diagnosis in these cases, with recognition of a focus of infection when regional lymph nodes are invaded. The primary lesion might be confused with syphilis, sporotrichosis. actinomycosis and epithelioma.

Thorough excision of the primary focus is recommended as the most effective treatment, with radium treatment for the lymphatic metastases; ultraviolet rays locally and with general irradiation are of value, and small doses of neoarsphenamin are useful in the treatment of tuberculids.

FURTHER OBSERVATIONS ON THE EPIDEMIOLOGY OF PEMPHIGUS NEONATORUM. R. R. MELLON and D. W. CALDWELL, Am. J. M. Sc. **169**:736 (May) 1925.

Human milk, often normally containing staphylococci, may be the source of some of the cases if these organisms are virulent for the child.

Staphylococci from any source are potentional causes of the epidemics observed, but are not necessarily found in the mother's milk, although the mothers found to be carriers had been segregated.

JAMIESON, Detroit.

URTICARIA SOLARIS. L. G. BEINHAUER, Arch. Dermat. & Syph. **12**:62 (July) 1925.

A case is reported of a man, aged 20, who developed severe urticaria whenever he was exposed to the rays of the sun or to those of the mercury vapor quartz lamp. The urticaria developed only on the exposed portions. He was of an "allergic family."

SENSITIZATION TO ADHESIVE PLASTER. W. P. BROWN, Arch. Dermat. & Syph. **12**:69 (July) 1925.

A case is reported of a woman subject to asthma who developed a marked skin reaction wherever a certain brand of adhesive plaster was applied.

JEANS, Iowa City.

ERYTHROEDEMA. J. S. FOWLER, Tr. M.-Chir. Soc. Edinburgh M. J. **36**:177 (Aug.) 1925.

Fowler chooses the name erythroedema, the Australian term for pink disease, which we in America designate as acrodynia. Fowler has seen four cases, all that have occurred in the Sick Children's Hospital of Edinburgh.

Feer of Zurich has called attention to a hitherto unnoticed symptom, that of high blood pressure.

Fowler's four cases had negative previous history, all the children having been healthy before the onset of the pink disease. A striking symptom in the nervous system is the marked muscular hypotonia without paralysis, and the reduced sensibility to pinpricks. All the children pulled at their hair. The writer enumerates the symptoms and features of the disease which are as follows:

The age is usually from the ninth month to the end of the second year.

The illness lasts about a year.

The mortality in ninety-one cases (Jeffreys Wood), five, chiefly from bronchial pneumonia. The hands and feet are characteristic, with cold, dusky, red and swollen skin, which the author describes as "sodden with perspiration and desquamating in little blisters." Secondary infection causes loss of nails or gangrene of the finger tips. There is profuse sweating with resultant rashes, and intolerable itching. There is wretchedness of the child with no interest in any amusement. Insomnia is characteristic.

It is the redness of the nose and cheeks that has suggested the name of pink disease. The mouth stays slightly open, due to muscular atony. Loss of teeth is common with secondary ulceration and sloughing of the gums.

Because of the muscular atony the child is limp and has a peculiar attitude. Photophobia makes him bury the face in the hands or pillow. Reflexes are absent or nearly so.

Fast pulse with high blood pressure are constant. Anorexia and salivation, albuminuria and pyuria may be present.

The disease is probably of infectious origin, either from the upper respiratory tract or from gastro-enteritis. Feer regards the disturbance as one of the vegetative nervous system. Nothing new is suggested in the treatment.

In the discussion Dr. Fowler answered the question as to the possibility of a primary origin in the teeth. He advises the roentgen-ray examination of the teeth early in subsequent cases for the purpose of learning the possible part their infection might play in the causation.

NEFF, Kansas City, Mo.

ERYTHEMATOSQUAMOUS AND FOLLICULAR ERUPTION DURING TREATMENT WITH ARSPHENAMIN. A. BOUTELIER, Bull. Soc. franç. de dermat. et syph. **32**:122, 1925.

An eruption resembling a lichenoid syphilid suddenly appeared after the sixth injection of neo-arsphenamin, in a boy, aged 7½ years, who had congenital syphilis. Following a seventh injection of the drug, it was aggravated. It had been preceded by pruritus, and was considered probably to be of arsenical origin.

SUBACUTE PEMPHIGUS WITH EXTENSIVE BULLAE IN A CHILD. PAUTIER, Bull. Soc. franç. de dermat. et syph. **32**:R.S.77, 1925.

The patient, a child, aged 5, was first seen by the author with a bullous eruption of four days' duration on the face and in the mouth. A few bullae subsequently appeared elsewhere, and there was fever and malaise. Silver compounds were applied to the denuded areas, and recovery ensued. Only staphylococci were found in the lesions. Keratitis was produced by inoculation in one rabbit, and reproduced by transfer to the cornea of another rabbit.

SYMMETRICAL ADENOMA SEBACEUM OF THE FACE AND RECKLINGHAUSEN'S DISEASE. PAYENNEVILLE, Bull. Soc. franç. de dermat. et syph. **32**:R.S.92, 1925.

In a girl, aged 10 years, adenoma sebaceum of the type described by Pringle co-existed with von Recklinghausen's disease, both conditions having first appeared at about the same. The same was true of a young soldier, who presented lesions of the Hallopeau type.

PARKHURST, Toledo.

CAMPHOR ERUPTIONS. R. LAMBRI, Policlinico **32**:941 (July 6) 1925.

Lambri reports a case of an itching urticaria after injections of camphorated oil in an adult, and a case in a child of an eruption, resembling scarlet fever, in pneumonia treated with camphor. Another child with grave debility from gastro-enteritis, given injections of camphor in ether, developed an eruption likewise, which subsided when the camphor was dropped.

[J. A. M. A.]

## Surgery and Orthopedics

MULTIPLE CARTILAGINOUS EXOSTOSIS. R. A. BLACK and A. S. TRAISMAN, Arch. Pediat. **42**:530, 1925.

This article deals with the condition of multiple cartilaginous exostosis, showing the familial, hereditary nature of the disease and presenting seven cases in one family in three generations. It is the only Jewish family with this condition described in the literature at any time. The proportion of males to females in this family is 5 to 2, the same proportion described in the literature by Ehrenfried and others. No definite etiologic factor is found to be present, although a history of syphilis and rickets is established. It was transmitted by an unaffected female.

VON MEYSENBUG, New Orleans.

CARDIOLYSIS FOR ADHERENT PERICARDIUM: CASE REPORT. A. S. LOE, Northwest Med. **24**:285 (June) 1925.

Loe reviews the history of cardiolysis and the literature of case reports on this subject. His own patient was a man, aged 58, who showed the physical findings of adherent pericardium, namely, (1) systolic retraction at the apex with

retraction of the epigastric angle, ribs or costal cartilages; (2) pulsus paradoxus with filling of the cervical veins on inspiration; (3) systolic retraction of the tenth and eleventh interspaces in the back; (4) diastolic shock; (5) immobility of the heart as shown by roentgen ray. Removal of a section of the third, fourth and fifth left ribs gave immediate and permanent relief to the patient.

SCOTT, Philadelphia.

TREATMENT OF INJURIES TO THE ELBOW IN CHILDREN. B. WHITECHURCH HOWELL, Brit. J. Child. Dis. **22**:116 (April-June) 1925.

The author takes up, in turn, I. Pulled Elbow (which just falls short of a dislocation of the head of the radius); II. Dislocations of the Elbow Joint, and III. Injuries to the Bones Around the Elbow Joint.

The complications of injuries to the elbow in children that are mentioned are the following: 1. Traumatic myositis ossificans. 2. Tubercle. 3. Volkmann's ischemic contracture. 4. Involvement of nerves. 5. Osteomyelitis. 6. Alteration of the "carrying angle." 7. Separation of the humeral epiphysis and fracture of the olecranon.

LANGMANN, New York.

THE RADICAL CURE OF HERNIA IN INFANTS AND YOUNG CHILDREN. GERTRUDE HERZFELD, Edinburgh M. J. **32**:281 (June) 1925.

Herzfeld has had a large experience in the surgical treatment of hernia, 2,100 cases during the last five years in the surgical outpatient department of the Royal Hospital for Sick Children. The incidence is as follows:

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|---|---|
| Inguinal | 1,843 — 88 per cent. |
| Umbilical | 250 — 12 per cent. |
| Femoral | 4 |
| Epigastric | 3 |
| Total | 2,100 |

Her paper deals with inguinal hernia, in which she discusses the objections to conservative treatment and the certain cure from operative treatment. She advises operation in every healthy infant, no matter how young, preferably under 6 months of age, at which time of life the general disturbance from operation is much less. She also advises a preliminary circumcision a few weeks before the herniotomy.

The main objection to the consent for operation on the part of the parents is the maintenance of the infant in the hospital during the convalescent period. The writer makes a point of the needlessness for keeping the child in the hospital longer than two or three hours after the operation. The infant is then taken home and the usual home feeding and care are not interrupted. Visits to the outpatient department or hospital are made from time to time during convalescence. Such children do not lose as much weight as those who are kept in bed at the hospital.

NEFF, Kansas City, Mo.

CYSTINURIA IN CHILDREN, WITH RENAL AND VESICAL CYSTIN CALCULI RESPECTIVELY. J. F. H. STALLMAN, Lancet **1**:375 (Aug. 22) 1925.

The first patient, a girl, aged 9¾ years, had complained of pain in the right side for a year. The urine showed a slight cloud of albumin, with blood cells and occasional pus cells and granular casts. The skiagram showed one large calculus and several smaller ones in the pelvis of each kidney. The urea concentration test and the analysis of the segregated urines showed a low renal efficiency and therefore a bad operative risk. Operation, however, was the only hope and was successfully done in two stages.

The second patient, a boy, aged 2 years and 7 months, had first screamed on passing water at the age of 10 months. These attacks of pain came every two weeks at first and more frequently later. The skiagram showed a large vesical calculus. A stone the size of a pigeon's egg was removed at operation. Two smaller stones were passed a year after operation and still later a large calculus was demonstrated in the left kidney.

The author states that cystinuria, when complicated by the formation of calculi, is undoubtedly a serious disease, both on account of the multiplicity of the stones and the serious damage to renal function thereby, and also on account of the persistence with which they continue to be formed. Their formation can evidently be controlled to a certain extent by the administration of large doses of sodium bicarbonate, but it is said to be largely independent of diet.

LANGMANN, New York.

OPERATIVE TREATMENT OF CONGENITAL PYLORIC STENOSIS. T. HOFFA, Monatschr. f. Kinderh. **30**:275, 1925.

Hoffa believes the Rammstedt operation to be the operation of choice. The majority of cases of pylorospasm will recover on medical and dietetic treatment. Those who do not respond may be cured by the Rammstedt operation.

GERSTLEY, Chicago.

A CASE OF PERFORATION OF MECKEL'S DIVERTICULUM. G. R. ULRICH, Ugesk. f. Læger **31**:664, 1925.

An infant, male, with a negative history until 8 months of age, suddenly became sick and passed blood by bowel from one to three times a day for four days. The blood in some instances was mixed with feces, but no mucus was present.

Examination of the abdomen at the time the patient was admitted to the hospital showed no palpable mass. A rectal exploration gave negative findings.

On the fourth day after admittance, the abdomen became distended and laparotomy was performed. Fresh blood was found in the abdominal cavity, the greater part of the intestine was distended, but no apparent signs of peritonitis were present. On the ileum, 75 cm. from the ileocecal valve, there was a 2.5 cm. long perforated Meckel's diverticulum. Resection, saline infusion and stimulants failed to save the child.

The cause of perforation is discussed as being due either to an ulcer of the peptic type or to disintegration of an area poorly nourished.

This condition may be differentiated from acute intestinal irritation and intussusception by the large amount of fresh blood.

SCHLUTZ, Minneapolis.

## Miscellaneous

EFFECT OF VARIOUS AGENTS — ULTRAVIOLET LIGHT, VACCINES, TURPENTINE, NEO-ARSPHENAMIN AND AUTO-BLOOD INJECTIONS — ON THE ENZYMES OF BLOOD AND SKIN. (A Preliminary Report.) J. F. SCHAMBERG and H. BROWN, Arch. Int. Med. **35**:537 (May) 1925.

Turpentine in olive oil (intramuscular), staphylococcic vaccines and auto-blood injections all tend to increase the lipolytic and proteolytic activity of the blood serum. Neo-arsphenamin in large doses depresses these serum activities while ultraviolet light decreases the lipolytic activity and increases the pro-

teolytic activity of the blood serum. The ultraviolet light also decreases the lipase and protease in an animal's skin. Distilled water in small doses decreases the lipolytic and possibly the proteolytic qualities of the blood.

JAMIESON, Detroit.

TRANSFUSION AND INJECTION OF BLOOD IN PEDIATRIC PRACTICE. A. HYMANSON, Arch. Pediat. **42**:440, 1925.

The various methods of transfusion are reviewed and a technic for the intramuscular injection of blood is given, which is as follows: Blood is taken from the arm of either parent with an ordinary Luer syringe and from 10 to 30 c.c. is injected into the muscle with great pressure, which is gently massaged for a few minutes to aid diffusion and absorption of the blood. In the diaper age it is perhaps best not to inject into the buttocks for fear of infection. The indications for blood injection are hemorrhage of the new-born, sepsis of the new-born, jaundice, severe athrepsia, simple anemia, von Jaksch anemia and leukemia.

VON MEYSENBUG, New Orleans.

EXPERIMENTAL PRODUCTION AND TRANSMISSION OF TAR SARCOMA IN CHICKENS. J. B. MURPHY and K. LANDSTEINER, J. Exper. Med. **41**:807 (June) 1925.

Injection of coal tar resulted in the production of spindle cell sarcoma in two instances, although attempts to transmit the neoplasm by filtrate or desiccate of the tumor were entirely unsuccessful.

JAMIESON, Detroit.

CHILD HYGIENE AND THE PHYSICIAN. GEORGE J. MOHR, Northwest Med. **24**:247 (May) 1925.

Mohr deplores the inadequate supervision of the development of the small child. He urges better prenatal care, adequate obstetric technic, insistence on breast feeding, a carefully controlled period of infancy, proper infant dietary, immunization methods, goiter prophylaxis, and frequent physical examinations of the preschool child.

SCOTT, Philadelphia.

OXYGEN THERAPY. H. W. DAVIES and A. R. GILCHRIST, Edinburgh M. J. **32**:225 (May) 1925.

These writers give their views about the indication for oxygen administration, the principles thereof and the methods. They condemn the ordinary tube and funnel inhalation as useless. An apparatus is described and illustrated which meets the objections to the other types now in use. Nasal tubes fit into the nostrils and a head band holds them in place, thus obviating the need of a constant attendant for this purpose. The rate of oxygen flow, whether fast or slow, does not interfere with the efficiency of their instrument. Much is now being written about oxygen therapy, and it is certain that better methods of administration will be welcomed.

NEFF, Kansas City, Mo.

INSULIN TREATMENT OF LEG ULCERS. FAURE-BEAULIEU and DAVID, Bull. et mém. Soc. méd. d. hôp. de Paris **49**:892 (June 12) 1925.

Ten of Faure-Beaulieu and David's patients with leg ulcers presented hyperglycemia, while no sugar was detected in the urine. They were treated with insulin, at a dose of 10 units injected subcutaneously twice a day. In one case the total amount of insulin was 1,600 units, usually, about 500 units. One woman

with an ulcer, 11 by 7 cm. in size, and glycemia of 2.12 gm., was cured in two months. She was given 480 units of insulin. A similar ulcer the year before took seven months to heal. Another woman with an ulcer, 7 by 9 cm. and glycemia of 2.41 gm. was completely cured in one month (320 units). One syphilitic woman had had a large and very painful ulcer for four years, rebellious to specific treatment. After two months' injections of insulin, the ulcer, 14 by 10 cm., was reduced by a half. The glycemia in this woman was 2.16 gm. per liter.

[J. A. M. A.]

CONGENITAL FRAGILITY OF THE BONES. U. FERRI, Pediatria **33**:20, 1925.

Ferri reports a case of osteogenesis imperfecta in a girl 4 months old, with multiple fractures of the long bones. Examination of the cerebrospinal fluid showed an ionized calcium content of 25 milligrams per 100 c.c. of fluid and no organic calcium. Ferri stresses the point that normally the cerebrospinal fluid should contain more organic than ionized calcium. After twenty-two irradiations with a quartz lamp, the ionized calcium was 28 mg. and the total calcium was 39 mg. per 100 c.c. of fluid. No further fractures occured after treatment with the quartz lamp was instituted.

DESANCTIS, New York.

STUDIES ON THE ABSORPTION AND EXCRETION OF DIFFERENT DYES IN RESPECT TO THE METHOD OF ADMINISTRATION. SOPHIE KAISER, Monatschr. f. Kinderh. **30**:286,1925.

The writer noticed that after intraperitoneal injections of saline solution there was a rapid elimination of water. In order to test this observation more accurately she tried injections of solutions of different dyes. The first experiments were with indigocarmin. In a first series twenty-one nurslings were given a total of eighty-one injections. In a later series ninety infusions in all were given to twenty-two children. The infusions were administered subcutaneously, intraperitoneally, intramuscularly, and intravenously.

The children seemed to be divided into two groups. By far the greater number excreted the dye when administered subcutaneously more slowly than when given intraperitoneally. In a smaller number the reverse was true. This phenomenon was not related, so far as could be determined, to the type of child. It might, however, be in some way related to the dye itself. Experiments were repeated with a number of other dyes, as for instance congo red, but the conclusions were not definite.

Observations were made to determine the rapidity of appearance of the dye in the duodenal contents. In 66 per cent. the dye appeared most rapidly after subcutaneous injection. Of course in such experiments the speed of absorption as well as the influence of the liver must be considered.

In order to avoid the confusion due to the dye itself, Kaiser then injected physiologic sodium chlorid solution intraperitoneally and subcutaneously and determined the amount and time of the excretion of the urine. Unquestionably, the intraperitoneal injections led to a greater and more rapid excretion. In fact, in some cases after intraperitoneal administration, more fluid was excreted than was injected.

The writer concludes from these experiments that the subcutaneous method of administering fluid is the one of choice.

GERSTLEY, Chicago.

# Book Reviews

PEDIATRICS OF THE PAST. By JOHN RUHRÄH, M.D. With a foreword by FIELDING H. GARRISON, M.D. Price, $10.00. Pp. 592, illustrated. New York: Paul B. Hoeber, Inc., 1925.

Previous to the appearance of this volume, little had been done in America to acquaint the medical profession with the pediatric thought of former centuries. The author has not attempted to deal with this as a whole but has, rather, selected gems of pediatric thought, and has translated for the reader the entire texts of those pediatric masters of the past whose contributions have been noteworthy and representative. With a broad-minded criticism he has pointed out the absurdities as well as the truths in each, but cautions the reader to deal leniently with the former since in all probability much that we now regard as proved will be discarded in the future.

Throughout, one is convinced not only of the author's knowledge of pediatrics and pediatric history, but of his broad grasp and application of medical history as a whole.

Extensively reviewed are the works of Hippocrates, Soranus of Ephesus, Aretaeus the Cappadocian, Oribasius, Aetius of Amida, Paul of Aegina, Rhazes, the pediatric incunabula, Paulus Bagellardus, Bartholomaeus Metlinger, Cornelius Roelans, Sebastian Oestereicher, Leonelli Faventide Victorius, Jonas and Raynalde, Thomas Phaer, Felix Wurtz, Hieronymus Mercurialis, Felix Platter, Guillaume de Baillou, Simon de Vallembert, Philip Gerhard Grüling, Francis Glisson, Robert Pemell, Francis Sylvius, Richard Wiseman, Sydenham, Mayow, Thatcher, Wolfgang Hoefer, Cadogan, Whytt, Rush, Beardsley, Soemmering, Armstrong, Underwood, Bard, the Heberdens, and Meissner.

Such an array is most formidable, but the arrangement and criticism is so delightfully executed that one may pick up this volume and read at random with pleasure and profit.

THE INTERNATIONAL YEAR BOOK OF CHILD CARE AND PROTECTION. Compiled by EDWARD FULLER, with a preface by the Marchioness of Aberdeen and Temair, LL.D. Price, $2.50. Pp. 565. New York and London: Longmans Green and Co., The World's Children, Limited, 1925.

This is the 1925 edition of this book, the first edition of which appeared in 1924. All new legislation and other facts are listed, and the world's governments' attitude toward the child and child care and protection is carefully detailed. As in the previous edition, this information is set down according to countries, arranged alphabetically. One who is interested in this subject owes much to the industry of the author.